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Original Articles

PREFACE

The contemporary evidenced based medical care has improved the quality of life by timely detection, proven therapeutic regimens and preventive measures. Along with the advancement of health sciences, there is an unmet need for the communication of medicine and biomedical research. The goal of our journal is to advance knowledge while improving the effectiveness of health care delivery, raise the social awareness of important health care issues and the translation of knowledge. The current issue of the MJHS presents a blend of quality articles covering topics in health sciences.

We take this opportunity to thank all of those who have contributed to the issue, and those clinician and researcher who, often on short notice, were kind enough to provide informed and valuable opinions on the submitted manuscripts. All the articles in this issue were thoroughly refereed, and we particularly thank the unnamed referees for their careful and timely job.

We hope our readers enjoy reading this issue of Majmaah Journal of Health Sciences and we look forward to receiving and publishing more high-quality scientific manuscripts.

Editor in Chief
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Updates on the Epidemiology, Pathophysiology and Management of Uraemic Pruritus

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ABSTRACT

Pruritus is a very common chronic and frustrating symptom that considerably affects the quality of life of patients with end-stage renal disease. The current review examined the updates in the epidemiology, pathophysiology, and management of uraemic pruritus. Recently, there has been reduction in the prevalence of urameic pruritus. With few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age, gender, and type of dialysis. However, pre-dialysis prevalence was lower than during dialysis prevalence. In recent years, new pathophysiologic hypotheses (immune and opioid) have been postulated and other hypotheses have been undermined (serotonin). There have been several anti-pruritic therapies examined among hemodialysis patients, including efficient dialysis, topical medications, systemic medications, physical and alternative treatments, and surgical treatments. However, none is considered the drug of choice or exclusively efficient in all patients. Several new medications have been examined in the last decade. However, for many of these medications, the evidence is still insufficient for their recommendations. After all advances in dialysis techniques and the availability of multiple therapies, uraemic pruritus is still a significant problem among hemodialysis patients that warrant further research.

Key words: Pruritus, uremia, kidney failure, renal dialysis, drug therapy

الملخص

الحكة هي عرض مزمن وشائع جدا لدى مرضى الفشل الكلوي النهائي وهي عرض محبط ويؤثر بشكل كبير على حياة المصابين به. هذه المراجعة تتعلق بدراسة التحديثات في الوبائية، والفسيولوجيا المرضية والعلاج للحكة الناتجة من ارتفاع البولينا. وجد مؤخرا انخفاض في معدل انتشار الحكة الناتجة من ارتفاع البولينا، كما وجد أنه ليس هنالك أي اختلافات كبيرة (مع وجود بعض الاستثناءات القليلة) في معدل انتشار الحكة بحسب السن والجنس ونوع الغسيل الكلوي. ومع ذلك فإن معدل انتشار الحكة قبل الغسيل الكلوي أقل من معدل الانتشار بعد الغسيل الكلوي. في السنوات الأخيرة، افترضت فرضيات فسيولوجية ومرضية جديدة (تتعلق بجهاز المناعة أو بالمادة الأفيونية) وقوضت فرضيات أخرى (السيروتونين). تم اختبار العديد من العلاجات المضادة للحكة وسط مرضى الغسيل الكلوي منها إجراء الغسيل بكفاء، الأدوية الموضعية، الأدوية الشاملة، العلاج الفيزيائي، العلاجات البديلة والعلاجات الجراحية. ومع ذلك لا يعتبر أي منها العلاج الأفضل أو الأكثر كفاءة لكل المرضى. خلال العقد الماضي تم اختبار عدة أدوية جديدة، ومع ذلك فإن الأدلة لاتزال غير كافية بالنسبة لكثير من هذه الأدوية لتتم التوصية بها. بعد كل التقدم في تقنيات غسيل الكلى وتوافر علاجات متعددة، لاتزال الحكة الناتجة من ارتفاع البولينا مشكلة كبيرة بين مرضى غسيل الكلى ويحتاج الأمر لمزيد من البحث.

INTRODUCTION

Pruritus is a very common chronic and frustrating symptom among hemodialysis patients. It affects the quality of life of patients with advanced or end-stage renal disease, because of the serious discomfort, sleeping disorders, anxiety and depression[1,2].

The pathophysiology is complex and incompletely understood. There are several anti-pruritic therapies examined among patients on maintenance hemodialysis. However, none is considered the drug of choice or exclusively efficient in all patients[1-3]. In the last 10 to 15 years, reduction in the prevalence of uraemic pruritus has been observed, new pathophysiologic hypotheses (immune and opioid) have been postulated, and multiple new medications have been examined. Therefore, we thought to review the new changes in the epidemiology,

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pathophysiology, and management of uraemic pruritus.

EPIDEMIOLOGY

Table 1 summarizes the prevalence of uraemic pruritus in studies published between 2000 and 2014. Although it is not easy to compare numbers between different studies due to differences in methodology, differences in pruritus definitions, and the small sample size of many of these studies, some findings can be pointed out. Studies published after 2000 had lower prevalence than studies published before 2000. In the current review, among the 24 studies examined (Table 1), the prevalence of uraemic pruritus ranged between 18% and 74%, with the majority of studies below 50%.[4, 5] For example, in a huge prevalence study (DOPPS) that examined more than 10,000 hemodialysis patients from Northern America, Western Europe, Japan, and Australia, the prevalence of uraemic pruritus was 42% using data collected between 2002 and 2003.[6] On the other hand, a non-comprehensive review for the prevalence studies published before 2000 showed prevalence between 22% and 86%, with the majority of studies above 50%.[7] It has been suggested that improving the quality of dialysis may have contributed to such reduction in the prevalence of uraemic pruritus.[8] There have been considerable geographic variability in the prevalence of uraemic pruritus. For example, in the DOPPS study, the prevalence of uraemic pruritus was lowest in France (36%) and highest in UK (50%).[6] In the 12 studies that calculated the prevalence by age and/or gender,[4,5,9-18] with few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age or gender. For the age, four studies showed significant association between the presence of pruritus and age, being higher in older age.[11,13,18,19] For the gender, two studies showed more prevalence in males[15,16] and one study showed high prevalence in females.[17] The prevalence of pruritus before dialysis was lower than the prevalence during dialysis (during the study).[4,16,17,20] This may be explained by the fact that pre-dialysis prevalence may indicate a lower stage of chronic kidney disease. In the few studies that examined the prevalence of uraemic pruritus among patients on hemodialysis versus peritoneal dialysis, no difference has been found in two studies[16,21] and one study found higher prevalence in hemodialysis compared with peritoneal dialysis.[22]

PATHOPHYSIOLOGY

Several hypotheses have been suggested to explain the underlying pathophysiology of uremic pruritus.[1-3] the presence of several pathophysiologic hypotheses for uremic pruritus is considered a consequence of the complex metabolism in uraemic patients and is considered an indication of inconclusiveness of any single hypothesis. Table 2 summarizes the main pathophysiologic hypotheses for uremic pruritus. These include:

Immune-inflammatory hypothesis: uraemic pruritus is believed to be a systemic inflammation rather than a local skin disorder.[7,23] This new hypothesis is supported by the overexpression of higher T helper-1 (TH1) cells, C-reactive protein and interleukin 6 (IL-6) in hemodialysis patients as well as the efficacy of specific immunomodulating therapies such as ultraviolet B phototherapy, thalidomide, and local tacrolimus in the treatment of uraemic pruritus.[1,24]

Opioid hypothesis: uraemic pruritus is believed to be associated with imbalances in the expression of mu and kappa opioid receptors that cause pruritus.[3] This new hypothesis is supported by the overexpression of mu-receptor agonist (beta-endorphin) to the kappa-receptor agonist (dynorphin-A) in patients with uraemic pruritus as well as the efficacy of nalfurafine, a centrally acting kappa-opioid receptor agonist, in the treatment of uraemic pruritus.[2,3]

Uraemic neuropathy hypothesis: uraemic pruritus is believed to be associated with diminished threshold of sensory perception, due to central sensitization to itch or due to peripheral nerve fiber damage.[1,2,25] This hypothesis is supported by the efficacy of anticonvulsant medications such as gabapentin and pregabalin in treating uraemic pruritus, through blocking neuronal calcium influx and decrease the release of neurotransmitters.[26]

Pruritogenic cytokines hypothesis: uraemic pruritus is believed to be associated with increased release of histamine and mast cells mediators, stimulating local itch receptors. This hypothesis is supported by the higher plasma histamine level[27] and the skin mast cell level[28] in patients with pruritus, without being linked to pruritus itself. Additionally, this hypothesis is supported by the efficacy of cromolyn sodium, a mast cell stabilizer, in treating uraemic pruritus. However,

Table 1: Prevalence of uraemic pruritus and its associations with age, gender, and type of treatment

Study	Number of patients	Age (years)	Country	Prevalence	Associations
Susel et al. (2014)[9]	200 HD	59.1	Poland	Overall: 75 (37.9%) Male: 49 (39.8%) Female: 26 (34.7%)*	No significant differences by age or gender
Tajbakhsh et al. (2013)[84]	100 HD	49 ± 12.3	Iran	Overall: 36/92 (39.1%)	None mentioned
Makhlough et al. (2013)[10]	153 HD	Yes: 59.6 ± 15.7 No: 61.7 ± 13.1	Iran	Overall: 94 (61.4%) Male: 48 (60%.0)* Female: 46 (63.0%)*	No significant differences by age or gender
Deshmukh et al. (2013)[85]	35 HD	48.8 ±13.4	India	Overall: 23 (65.7%)	None mentioned
Lopes et al. (2012)[11]	980 HD	No: 47.6± 14.3 Mild: 49.6±14.1 Severe: 51.2±13.5	Salvador & Brazil	Overall: 429 (43.8%) Severe: 190 (19.4%)	Pruritus was significantly associated with older age but not gender
Welter et al. (2011)[12]	105 HD	51.9	Brazil	Overall: 46 (43.8%) Severe: 9 (19.6%)	No significant differences by age or gender
Falodun et al. (2011)[86]	Total : 120 HD: 76 Conservative: 44	43.1±15.4	Nigeria	Overall: 32 (26.7%) HD: 21 (27.6%) Conservative: 11 (25.0%)	No significant differences between the treatment groups
Attia et al. (2010)[19]			Egypt	Overall: 66 (32.0%) Adult: 58 (35.6%) Children: 8 (18.6)	Pruritus was significantly higher among adults* and diabetics but not HCV
Khanna et al. (2010)[20]	Total: 200 CKD: 150 HD: 50	40.2±15.2	India	Overall: 72 (36%) No dialysis: 43 (28.7%)* Dialysis: 29 (58.0%)*	Significantly higher in CKD with dialysis than CKD without dialysis*
Yong et al. (2009)[21]	Total: 179 PD: 107 HD: 27 Palliative: 45	61.9 ±12.3	Hong Kong	Overall: 114 (63.7%) PD & HD: 88 (65.7%) Palliative: 26 (57.8%)	No significant differences between the treatment groups
Melo et al. (2009)[13]	101 HD	Yes: 54.0 No: 38.5	Brazil	Overall: 31 (30.7%) Males: 19 (32.2%)* Females: 12 (28.6%)*	Pruritus was significantly associated with older age but not gender
Layegh et al. (2007)[22]	Total: 127 HD: 93 PD: 34	HD: 48 PD: 42	Iran	Before dialysis: 60 (47.2%)* Overall dialysis: 70 (55.1%) HD: 59 (63.4%) PD: 11 (32.3%)	Significant differences by type of dialysis (HD>PD)
Resic et al. (2007)[14]	77 HD	55.8 ± 14.1	Bosnia & Herzegovina	Overall: 45 (58.4%) Male: 26 (63.4%)* Female: 19 (52.8%)*	No significant differences by age or gender*

Study	Number of patients	Age (years)	Country	Prevalence	Associations
Pisoni et al. (2006)[6]	DOPPS 1: 10810 HD DOPPS 2: 10265 HD	Yes: 60.7±14.5 No: 60.3 ± 14.6	DOPPS 1: 7 Western countries DOPPS 2: 12 Western countries	Moderate-severe pruritus DOPPS 1: 45% (38-48%) DOPPS 2: 42% (36-50%)	Significant differences by country (36% in France and 50% in UK) and between facilities (5–75%)
Narita et al. (2006)[15]	1773 HD	60.2±12.8	Japan	Moderate-severe pruritus* Overall: 947 (53.4%) Male: 609 (58.3%) Female: 338 (46.5%)	Significant difference by gender (males > females) but not by age
Udayakumar et al. (2006)[87]	100 HD	10-76	India	Overall: 53 (53.0%)	None mentioned
Duque et al. (2006)[88]	105 HD	48±11	USA	Overall: 60 (57.1%)	None mentioned
Mistik et al. (2006)[16]	Total: 341 HD: 289 PD: 52	51.1±15.0	Poland	Before dialysis: 97 (28.4%) Overall dialysis: 177 (51.9%) HD: 145 (50.2%) PD: 32 (61.5%)	Significant difference by gender (63.8% in males vs. 36.2% in females) but not by age or type of dialysis
Dyachenko et al. (2006)[5]	70 HD	62.9 ± 14.1	Israel	Overall: 52 (74.3%)	No significant differences by age, gender or ethnicity
Zucker et al. (2003)[4]	219 HD	62 ± 13.7	Israel	Before dialysis: 40 (18%) During dialysis: 105 (48%)	No significant differences by age or gender
Szepietowski et al. (2002)[17]	130 HD		Poland	Before dialysis: 47 (36.2%) During dialysis: 53 (40.8%)	Significant gender difference (females > males) but no age difference
Subach and Marx (2002)[89]	70 HD			Overall: 49 (70.0%)	None mentioned
Silverberg et al. (2001)[90]	Total: 30 HD: 16 Transplant: 10 Medical: 4	14 (3-18)	USA	Overall: 17 (56.7%) HD: 11 (69%) Transplant: 5 (50%) Medical: 1 (25%)	No significant differences between the treatment groups *
Jamal and Subramanian (2000)[18]	100 HD	13-80	Saudi Arabia	Overall: 67 (67.0%) Males: 27 (67.5%) Females: 40 (66.7%)	Significant age difference (older > younger)* but no overall gender difference

*Calculated from the published data HD: on hemodialysis, PD: on peritoneal dialysis; Yes: patient has pruritus
No: No pruritus

the limited efficacy of classical antihistamines (cetirizine, loratadine, and desloratadine) in treating uraemic pruritus draws doubt over the role of histamine in uraemic pruritus.[1,2]

Skin alteration hypothesis: skin xerosis is believed to promote uraemic pruritus by lowering the perception threshold.[29] This hypothesis is supported by the efficacy of skin emollients in relieving mild and/or localized uraemic pruritus.[30,31]

Uraemia-related alterations hypothesis: uraemic pruritus is believed to be associated with severe secondary hyperparathyroidism, hyperphosphatemia, and elevated calcium–phosphate product.[1,3] Additionally, the serum parathyroid hormone has been shown in some studies to correlate with the severity of pruritus in hemodialysis patients.[10] This may lead to deposition of calcium phosphate crystals in the epidermis, producing peripheral sensitization to itch. This hypothesis is supported by the improvement of uraemic Pruritus after parathyroidectomy.However, the lack of correlation between preoperative levels of calcium, phosphate, and calcium-phosphate product in these patients and pruritus add to the inconclusiveness on this hypothesis.[32]

Serotonin hypothesis: Serotonin that is known to enhance pain perception and pruritic symptoms has been shown to be higher in dialyzed patients, especially those with pruritus, but not linked to pruritus.[33] Therefore, it has been believed that uraemic pruritus is associated with higher serotonin activity. However, the inefficacy of serotonin antagonists as ondansetron in treating uraemic pruritus undermines the serotonin hypothesis.[34]

MANAGEMENT

Similar to the multiple hypotheses suggested to explain the pathophysiology of uraemic pruritus, several anti-pruritic therapies have been examined in hemodialysis patients. However, none is considered the drug of choice or exclusively efficient in all patients.[1-3] Additionally, most available evidence and recommendations are based on limited-quality research in the form for small RCT, uncontrolled trials, pre and post small interventional studies, and case series. Therefore, there are no current standard guidelines. The available therapies published between 2000 and 2014 are discussed here. These include;

- Treatments of uraemia such as adequate dialysis, optimization of metabolic parameters, and renal transplantation which is considered the definitive treatment
- Evidence from a well-conducted trial at one or more institutions
- Topical treatments such as emollients, topical analgesics, and tacrolimus
- Systemic pharmacologic treatments such as antihistamines and mast cell stabilizers, anticonvulsants, opioid receptor medications, serotonin antagonists, antidepressants, and other medications. Table 3 summarize the local and systemic pharmacologic agents.
- Physical and alternative treatments such as phototherapy and acupuncture
- Surgical treatment such as parathyroidectomy

Adequate dialysis: It has been shown that increasing the dose of dialysis may improve pruritus.[32] Additionally, in some studies, higher dialysis efficacy, as expressed by dialyzer clearance, volume distribution of area, and dialysis duration (Kt/v), has been inversely associated with uraemic pruritus.[5,36] However, the lack of association between dialysis efficacy and the degree of pruritus in other studies may be explained by the fact that Kt/v actually quantify urea clearance and does not quantify the removal of mid- and large-sized molecules which may be responsible for uremic pruritus.[15] Interestingly, switching dialyzed patients to polymethylmethacrylate based dialysis membranes (PMMA) has been associated with a significant reduction in the degree of pruritus, irrespective of dialysis efficiency or improvement in other biochemical parameters.[37,38] Although the exact mechanism is not known, it may be due the ability of the PMMA dialyzers to adsorb solutes such as cytokines and some cationic compounds. However, since the evidence has been based on generally small non-randomized studies, the finding should not been overestimated. Additionally, uraemic pruritus is still prevalent problem in the US where almost all patients are already dialyzed against PMMA.[39,40]

Topical treatments: As mentioned above, skin xerosis is believed to promote uraemic pruritus.[29] Therefore emollients with high water content are widely used topical treatment of uremic pruritus, especially if

Table 2: Pathophysiologic hypotheses of uraemic pruritus and related medications

Hypotheses	Mechanism and mediators	Related medications
Immune-inflammation: uraemic pruritus is caused by systemic inflammation rather than a local skin disorder	Higher T helper-1 (TH1) cells, C-reactive protein and interleukin 6 (IL-6) in uraemic pruritus	Immunomodulating therapies: Ultraviolet B phototherapy, thalidomide, tacrolimus
Opioids: uraemic pruritus is associated with imbalances in the expression of mu and kappa opioid receptors	Overexpression of mu-receptor agonist (beta-endorphin) to the kappa-receptor agonist (dynorphin-A) was observed in patients with uraemic pruritus	Kappa-opioid receptor agonist: Nalfurafine Mu-opioid receptor antagonist: Naltrexone
Neuropathy: uraemic pruritus is associated with diminished threshold of perception, due to central sensitization to itch or due to peripheral nerve fiber damage	Increased neuronal calcium influx and increased release of neurotransmitters	Anticonvulsants: Gabapentin and pregabalin
Pruritogenic cytokines: uraemic pruritus is associated with increased release of histamine and mast cells mediators, stimulating local itch receptors	Increased histamine produced by mast cells, keratinocytes, and leukocytes. Increased release of mast cell mediators including histamine, IL2, acethylcholine, TNF-α and proteases.	Classical antihistamines: Cetirizine, loratadine, and desloratadine. Mast cell stabilizer: Cromolyn sodium
Skin alteration: skin xerosis promote uraemic pruritus by lowering the perception threshold	Skin xerosis is caused by decrease in sweat volume, atrophy of sebaceous glands, and dermal dehydration	Topical emollients
Uraemia-Related Alterations: uraemic pruritus is associated with severe secondary hyperparathyroidism, hyperphosphatemia, and elevated calcium–phosphate product	Calcium phosphate deposits in the epidermis produce peripheral sensitization to itch	Treatment of hyperparathyroidism: vitamin D and calcimimetics Surgical parathyroidectomy
Serotonin: uraemic pruritus is associated with higher serotonin activity	Serotonin enhances pain perception and pruritic symptoms through 5-HT3 receptors on the nervous system	Serotonin antagonists: ondansetron and granisetron

xerosis is present on examination. Despite the limited data quality being uncontrolled or non-randomized small-sized studies, emollients have been shown to be a safe and effective initial treatment for uaemic pruritus.[30-31] Topical use of gamma-linolenic acid has been shown to be effective and safe adjuvant agent for refractory uremic pruritus.[41] Although the study was RCT, the small number of studied patients and the lack of other confirmatory evidence, may limit its recommendation at this point. Local use of pramoxine, an analgesic, has been shown in a pharmaceutically-sponsored RCT to be a safe and convenient therapy for hemodialysis patients with persistent moderate to severe pruritus despite appropriate use of emollients.[42] Local use of capsaicin, another analgesic, has been shown to be effective in one recent RCT[43] and ineffective in another earlier interventional study.[44] This conflicting data and being suggested for localized pruritus rather than systemic one may limit its current recommendation. Finally, the earlier efficacy of short-term topical use of tacrolimus ointment in reducing uaremic pruritus[45,46] has not been replicated in a recent RCT.[47] Additionally, the fear from the carcinogenic properties of systemic use of tacrolimus and its relatively high cost limit its use, if any.[45,46]

Antihistamines: Although they are probably the most widely prescribed systemic medications in pruritic diseases including uraemic pruritus, the findings from recent studies are not supportive. Classical antihistamines (cetirizine, loratadine, and desloratadine) have been shown to have no or limited efficacy in controlling uraemic pruritus.[34,48,49] On the other hand some medications with antihistaminic properties and mast cell stabilizers showed promising results. For example, doxepin, a tricyclic antidepressant with anti-H1 receptor effect,

Table 3: Pathophysiologic hypotheses of uraemic pruritus and related medications

Treatment	Studies	Number of patients	Level of evidence	Efficacy	Safety	Comments
TOPICAL TREATMENTS						
Emollients	Okada & Matsumoto (2004)[30]	20	3	Yes	Yes	Effective safe initial treatment but insufficient evidence
	Szepietowski et al. (2005)[31]	19	4	Yes	Yes	
Gamma-linolenic acid	Chen et al. (2006)[41]	17	1	Yes	Yes	Promising probably effective treatment but no sufficient evidence yet
Pramoxine	Young et al. (2009)[42]	28	1	Yes	Yes	
Capsaicin	Weisshaar et al. (2003)[44]	11	3	No	Yes	Conflicting efficacy data. Insufficient evidence
	Makhlough et al. (2010)[43]	34	1	Yes	Yes	
Tacrolimus	Pauli-Magnus et al. (2000)[45]	3	6	Yes	Yes	Conflicted efficacy data and possibility of carcinogenic effect. Not recommended
	Kuypers et al. (2004)[46]	25	4	Yes	Yes	
	Duque et al. (2005)[47]	22	1	No	Yes	
ANTIHISTAMINES AND MAST CELL STABILIZER						
Cetirizine	Weisshaar et al. (2004)[34]	21	4	No	Yes	Widely used despite lack or limited efficacy
Loratadine	Legroux-Crespel et al. (2004)[48]	52	4	No	Yes	
Doxepin	Pour-Reza-Gholi et al. (2007)[50]	24	1	Yes	Yes	
Desloratadine	Marquez et al. (2012)[49]	22	3	Modest	Yes	Promising safe and effective treatment but no sufficient evidence yet
Cromolyn	Rosner (2006)[51]	2	6	Yes	Yes	
	Vessal et al. (2010)[28]	62	1	Yes	Yes	
ANTICONVULSANTS						
Gabapentin	Gunal et al. (2004)[52]	25	1	Yes	Yes	Effective for resistant pruritus unresponsive to antihistamines and emollients and associated with peripheral neuropathy. Adverse reaction may be an issue
	Manenti et al. (2005)[53]	6	6	Yes	Yes	
	Naini et al. (2007)[54]	34	1	Yes	Yes	
	Razeghi et al. (2009)[55]	34	1	Yes	Equivocal	
	Solak et al. (2012)[56]	50	1	Yes	Equivocal	
	Marquez et al. (2012)[49]	22	3	Marginal	No	
	Rayner et al. (2012)[59]	71	4	Yes	Equivocal	
Pregabalin	Aperis et al. (2010)[57]	16	4	Yes	Equivocal	An equally effective alternative drug to gabapentin used for resistant pruritus with probably lower adverse reactions
	Solak et al. (2012)[56]	50	1	Yes	Equivocal	
	Rayner et al. (2012)[59]	15	4	Yes	Yes	
	Shavit et al. (2013)[26]	12	4	Yes	Yes	
	Yue et al. (2014)[58]	188	1	Yes	Yes	
K-OPIOIDS AGONIST						
Naltrexone	Pauli-Magnus et al. (2000)[61]	23	1	No	No	Naltrexone is ineffective in treating uraemic pruritus and has frequent GIT adverse effects. Not recommended
	Legroux-Crespel et al. (2004)[48]	52	1	No	No	

Nalfurafine	Wikstrom et al. (2005)[62]	144	1	Yes	Yes	Nalfurafine is a safe and effective treatment for uremic pruritus refractory to conventional therapies
	Kumagai et al. (2010)[63]	337	1	Yes	Yes	
	Inui et al. (2012)[65]	6	4	Yes	Yes	
	Kumagai et al. (2012)[64]	211	4	Yes	Yes	
SEROTONIN ANTAGONISTS						
Ondansetron	Ashmore et al. (2000)[67]	16	1	No	Yes	Ondansetron is ineffective in treating pruritus and should not be recommended.
	Murphy et al. (2003)[68]	24	1	No	Yes	
	Deshpande (2004)[66]	1	6	Yes	Yes	
	Yue et al. (2014)[58]	188	1	No	Yes	
Granisetron	Albares et al. (2003)[69]	1	6	Yes	Yes	Granisetron is probably effective but no sufficient evidence yet
	Layegh et al. (2007)[22]	14	4	Yes	Yes	
NOVEL AND OTHER THERAPIES						
Sertraline	Shakiba et al. (2012)[70]	19	4	Yes	Yes	Promising safe and effective medication but no sufficient evidence yet
	Chan et al. (2013)[71]	20	4	Yes	Yes	
Montelukast sodium	Nasrollahi et al. (2007)[72]	16	1	Yes	Yes	
Omega-3 fatty acids	Begum et al. (2004)[73]	22	1	No	Yes	
	Ghanei et al. (2012)[74]	22	1	Yes	Yes	

has been shown in one RCT as effective systemic treatment against resistant uraemic pruritus.[50] The main adverse effect doxepin was temporary drowsiness. Additionally, cromolyn sodium, a mast cell stabilizer has been shown in one RCT and a case report as very effective and safe medication for uraemic pruritus.[28,51]

Anticonvulsants: Gabapentin is an anticonvulsant medication used in a variety of neuropathic pain syndromes. Several RCTs and one case series over the last 10 years showed its clear effective management of uraemic pruritus.[49,52-56] The studied patients typically had resistant uraemic pruritus unresponsive to emollients and antihistamines with the majority having additional neurologic problems.[55] The safety of gabapentin has been generally acceptable,[52-54] although in some recent studies has been questionable.[49] Common adverse effects included somnolence, dizziness and fatigue.[49,56] Therefore it has been suggested to gradually use the lowest effective dose to avoid adverse effects.[34] Pregabalin is very similar to gabapentin regarding the structure and mechanism of action.[26] Its effectiveness against resistant uraemic pruritus has been shown in recent RCTs and observational studies.[26, 56-59] Pregabalin has been suggested as an equally effective alternative drug to gabapentin in patients with resistant uraemic pruritus, with probably more rapid effect and with better tolerability.[56,59] Dizziness and somnolence were the most common side effects for pregabalin use.[56,57,59]

Opioid receptor medications: Although initially suggested as an effective treatment of uraemic pruritus,[60] naltrexone, a mu-receptor antagonist, has been shown in 2 recent RCTs as ineffective medication for uremic pruritus.[48,61] Additionally, naltrexone is expensive and accompanied by a high incidence of gastrointestinal side effects.[48,61] Therefore naltrexone should not be currently recommended for uraemic pruritus. Nalfurafine is a recently developed selective

kappa-opioid receptor agonist with a potent antipruritic effect on various types of pruritus. Two recent large RCT[62,63] and two interventional studies [64,65] showed its effectiveness in reducing itch in hemodialysis patients with uremic pruritus refractory to conventional therapies. The most common side effect of nalfurafine was insomnia, seen in only approximately 10% of patients.

Serotonin antagonists: In a pediatric case report, the use of ondansetron was followed by a dramatic improvement of resistant uraemic pruritus, unresponsive to antihistamines.[66] However, a recent large RCT[58] and another two smaller RCTs[67,68] consistently showed negligible effects of ondansetron in treating uraemic pruritus, and therefore, should not be recommended for uraemic pruritus. Granisetron has been shown to be effective against moderate to severe uraemic pruritus.[22,69] However, the limited quality of data and small number of examined patients preclude current recommendation of granisetron. Inconsistent data about the role of serotonin antagonists in controlling uraemic pruritus undermine the serotonin hypothesis to explain the pathophysiology of uraemic pruritus.

Novel and other medications: Few additional drugs have been suggested as a promising anti-pruritic agents but the current data quality does not allow its current recommendations. Sertraline, antidepressant that has been used for the treatment of non-renal pruritus, has been found to be effective for antihistamine-refractory uremic pruritus in renal palliative care patients.[70,71] However, since the available data were based on small uncontrolled studies, confirmation of these findings in RCTs is required before its recommendation. One small-sized RCT found montelukast, a leukotriene receptor antagonist, safe and effective medication in the treatment of uremic pruritus not responding to the currently available antipruritus medications.[72] Finally, two RCTs showed conflicting data about the efficacy of omega-3 fatty acids for treatment of itching in hemodialysis patients.[73,74]

Parathyroidectomy: Despite the lack of correlation between pruritus and preoperative levels of calcium, phosphate, and calcium-phosphate product, parathyroidectomy has been associated with significant improvement of pruritus among 37 patients on hemodialysis who suffered from secondary hyperparathyroidism.[32] Additionally, medical treatment of hyperparathyroidism using calcimimetics has been associated with reduced itching among hemodialysis patients.[75]

Ultraviolet-based therapy: Ultraviolet irradiation has been used in treating various types of pruritus, including uraemic pruritus.[76] The exact mechanism is not exactly known but a decrease in proinflammatory cytokine levels and induction of mast cell apoptosis have been suggested.[77] Two cases series and one interventional study showed beneficial effect of narrowband ultraviolet B phototherapy in alleviating renal pruritus.[78-80] However, the same results could not be replicated in a small recent RCT.[81] Additionally, the possibility of recurrence, the risk of long-term carcinogenic effect, and the interaction with concomitant immunosuppressive therapy should be weighted before starting ultraviolet B phototherapy for renal patients with pruritus.[79-80]

Acupunture: A recent systematic review of 3 RCTs and three uncontrolled observational studies found acupunture as an easy, safe and effective means of relieving uraemic pruritus.[82] However, these studies had a significant design flaw and high risk of bias, which make the current evidence insufficient to recommend acupuncture for treatment for uraemic pruritus.

Suggested step-wise treatment: Due to current lack of standard guidelines for the management of uraemic pruritus, several authors proposed a step-wise approach in treating patients with uraemic pruritus.[3,24,83] Initial therapy should include more efficient dialysis and topical emollients and/or analgesics (such as pramoxine lotion). Resistant pruritus not responding to previous treatment should be started on oral antihistamines and if not sufficient then oral anticonvulsants as gabapentin or pregabalin. Refractory pruritus not responding to previous treatments should be started on intravenous nalfurafine, ultraviolet B phototherapy, or other novel medications that did not have sufficient evidence for current recommendations.

CONCLUSION

The prevalence of uraemic pruritus has been reduced in recent years. Although still complex, recent years

improved our understanding in the pathophysiology of uraemic pruritus. Several new medications have been examined in the last decade. However, in many of these medications, the evidence is still insufficient for their recommendations. After all advances in dialysis techniques and the availability of multiple therapies, uraemic pruritus is still a significant problem among hemodialysis patients that warrant further research.

KEY POINT BOX

- With few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age, gender, and type of dialysis.
- Although still complex, recent years improved our understanding in the pathophysiology of uraemic pruritus.
- We reviewed the available therapies published between 2000 and 2014, and we conclude that uraemic pruritus is still a significant problem that warrant further research.

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Clinical Characteristic and Lingering Challenges of Umbilical Cord Blood (UBC) Banking: Future Perspective to Improve Quality of Hematopoietic Stem Cells (HSC)

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ABSTRACT

Both in malignant and non-malignant disorders stem cell based therapies are increasingly being utilized with promising results. hematopoietic reconstitution comprises mainly of 3 types of cells bone marrow (BM), peripheral blood (PB), and umbilical cord blood (UCB). The readily available and abundant resource of stem cell is umbilical cord blood. However, the typical single UCB unit could fetch relatively low numbers of hematopoietic stem- and progenitor cells (HSPCs) and the associated delay in procuring them restrict its routine applicability. In the past decade, the clinical applications of UCB-based cell therapies have broadened with a growing number of diseases treated with hematopoietic stem cell (HSC) transplantation. The assessment of UCB unit hematopoietic stem cells (HSCs), such as CD34+ cells or CFUs (Colony forming units), may provide a more direct estimate of the hematopoietic potential of the unit than the TNC count. As interlaboratory standardization of these assays has been achieved, the selection of UCB units for banking based on quantitation of hematopoietic progenitors is currently not feasible. However, CFU assays provide the only reliable assessment of the viability of the CB unit, although great efforts have been made to develop flow cytometry methods for viability staining. Despite of extreme efforts to find strategies that would enable the *ex vivo* amplification of stem cells for transplantation globally, it has been proven difficult to culture the HSCs in the labs. Therefore, it is imperative to have clear understanding regarding integration of HSC self-renewal, proliferation, and differentiation, molecules participating in their regulation and clinical benefit after their modification. Attempts have been made to improve the quality of UCB units through e.g. standardization of bank procedures, of stem cell enumeration, and of the assessment of HPCs viability. Over 4000000 UCB units are currently available in international registries. However, a significant proportion of patients is still left without a suitable donor, necessitating further development of UCB banking process.

Key words: Umbilical Cord Blood; hematopoietic stem cells

الملخص

لوحظ في الاونة الاخيره تزايد استخدام العلاج بالخلايا الجذعية للقضاء عى اضطرابات الاورام الحميدة و الخبية منها, وظهور نتائج طبية واعدة من خلال إعادة مكونات الدم عن طريق ثلاثة انواع وهي : خلايا نخاع العظم، و الدم المحيطي ، ودم الحبل السري. ومن اكثر الموارد المتاحة بسهولة ووفرة هي الخلايا الجذعية من دم الحبل السري. ومع ذلك، فان وحدة واحدة نموذجية من دم الحبل السري تعطي اعداداً قليلة نسياً من الخلايا الاصلية والخلايا الجذعية المكونة للدم, حيث تاخر تطبيق الحصول على هذه الاعداد القليلة مع وجود الاجراءات الروتينية الكثيرة خلال العقد الماضي. ومع تزايد اعداد الامراض سعت التطبيقات الاكلينيكية استناداً للوحدة النوذجية للعلاج من خلال زراعة الخلايا الجذعية المكونة للدم. ان عملية تقييم الوحدة النموذجية للخلايا الجذعية لمكونات الدم مثل ترميز جينات البروتين (CD34) بالاضافة الى وحدات تشكيل المستعمرات من الفطريات والبكتيريا (CFUs) قد توفر تقديرات مباشرة اكثر من احصاء مجموع انوية الخلية (TNC). وتم العمل على توحيد هذه القياسات بين المختبرات. اما عملية اختيار الوحدات النموذجية للخلايا الجذعية وتخزينها وحفظها على أساس الكميات المكونة للدم هي حالياً غير مجدية. ومع ذلك، فعملية فحوصات وحدات تشكيل المستعمرات من الفطريات والبكتيريا (CFUs) توفر تقييم موثوق وأجدى من وحدة دم الحبل السري، على الرغم من أنه قد بذلت جهود كبيرة لتطوير طرق قياس التدفق الخلوي لبقاء التلوث, وعلى الرغم من الجهود المضنية لإيجاد استراتيجيات من شأنها أن تمكن من استخدام زراعة الخلايا الجذعية بشكل اوسع على الصعيد العالمي، فقد ثبت عملياً أنه من الصعب نشر ثقافة الخلايا الجذعية لمكونات الدم في المختبرات. ولذلك، فمن الضروري أن يكون هناك فهم واضح بشأن دمج الخلايا الجذعية لمكونات الدم مع التجديد الذاتي، والانتشار، والتمايز، والجزيئات المشاركة في تنظيمها والاستفادة الاكلينيكية بعد تعديلها. وقد بذلت محاولات لتحسين نوعية وحدات دم الحبل السري من خلال- على سبيل المثال- توحيد معايير وأعداد واجراءات حفظ وتخزين الخلايا الجذعية، وتقييم قدرتها على البقاء. فهناك اكثر من (4000000) وحدة من الخلايا الجذعية المكونة للدم متاحة حالياً في السجلات الدولية ومع ذلك، ما زال هنالك نسبة كبيرة من المرضى تترك لعدم وجود متبرع مناسب، مما يستدعي مواصلة تنمية وتطوير عملية حفظ وتخزين الخلايا الجذعية للحبل السري.

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INTRODUCTION

Stem cells exist in a wide array of plasticity and self-renewing abilities, from embryonic stem cells that can divide indefinitely and recapitulate the entire organism to adult stem cells, which are limited to a few cell divisions and differentiation into a small number of cell types; each stem cell has its niche both in the life of the animal and in the world of therapeutic medicine. Umbilical cord blood is a widely available, often discarded source of stem cells. This population of stem cells has the potential to be an intermediate population between the naïve embryonic stem cell and the less plastic adult stem cell. Owing to its immature source, umbilical cord blood derived stem cells may be a more malleable population of stem cells with less of the inherent risk of tumor formation found in embryonic stem cells.[1]

Human umbilical cord blood is the blood found in the blood vessels of umbilical cord and placenta. The cord blood is regarded as the "life line" that supplies the developing fetus with the important nutrition elements and oxygen required for proper fetal development. Beside its role in development, umbilical cord blood has been also involved in therapeutic applications, which reported for the first time in 1972, by the pioneer doctors in the United States, Ende and Ende, to treat a patient of acute lymphoblastic leukemia.[1] It was later used regularly for transplantation in hematology setting for bone marrow replacement, following either hematological malignancy or bone marrow failure after any chemotherapy. Umbilical cord blood was, for many years, considered to be restricted to blood disease therapy.[2,3] However, advances in the production of tissue groups, from the three germ layers, has highlighted the additional potential of umbilical cord blood in treatment of other pathological disorders and medical applications including regenerative medicine and tissue engineering.[4-7]

Umbilical cord blood offers an alternative source of stem cells with both research and clinical advantages over other sources of stem cells. Moving toward effective clinical applications requires a readily abundant supply of stem cells to provide the needed amounts of stem cells. With the global birth rate reaching 200 millions/year, umbilical cord blood can be considered as one of the most abundant sources of stem cells.[4,5] In addition, unlike embryonic stem cells, umbilical cord blood stem cells collection does not raise any ethical or religious concerns, which makes it more appealing to both the research and clinical fields.[5,6,8]

Stem cell-based therapy

Given their role in tissue maintenance and repair, stem cells are prime targets for regenerative medicine. The hematopoietic system's liquid nature and underlying easy delivery of HSC to their host tissue has made HSCs the prototype of organ regenerating stem cells and the paradigm for other stem cell-based therapies. Transplantation of HSCs is a conceptual and elegant example of stem cell therapy, and provides means to treat hematopoietic malignancies such as leukemias, lymphomas and immunodeficiencies. The beginning of hematopoietic cell transplantation (HCT) dates back to the late 1950's but clinical success and subsequent breakthrough came with the discovery of the human leukocyte antigen (HLA) system and the selection of immunologically compatible donors in the beginning of the 70's.[9] The basis for this prototype of cellular therapy is the treatment with radio- and/or chemotherapy to breakdown the patient's own hematopoietic system, followed by infusion of new stem- and progenitor cells, which gradually reestablish hematopoiesis.[9]

The time to donor engraftment, also called time to neutrophil recovery (TNR) or immune reconstitution, is a critical period as it leaves the patient susceptible to infection with increased risk of transplant-related mortality. hematopoietic cell transplantation (HCT) can either be autologous, re-infusing the patient's own HSCs; or allogeneic, involving a donor, which in turn can be related or unrelated. The success of allogeneic transplantations greatly depends on the degree of immunological compatibility between donor and recipient tissues as mediated by the HLA genes, and the related occurrence of graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) effect.[10,11] Traditionally, all stem cell transplants performed used BM as sole source of HSCs.

Today, HSCs obtained from mobilized peripheral blood (mPB) are more commonly used[12]. HSC mobilization can be achieved with e.g. chemotherapy, the cytokine granulocyte colony-stimulating factor (G-CSF) and/or AMD3100, a drug that inhibits binding of the homing molecule CXCL12 to its receptor CXCR4.[13,14,15]

Umbilical cord blood as a third stem cell source was introduced in 1988. Whenever possible, the choice of HSC source is tailored to meet the needs of each individual patient, as they differ with respect to engraftment potential and kinetics, immunogenic characteristics, as well as development and severity of GVHD.[16,17]

Classification of stem cells according to their origin

The use of different definitions and terminology, in scientific and other literature, is often confusing. It is to be expected that as stem cell research progresses, more accurate nomenclature will develop. Stem cells may be derived from fluids and tissues from the moment of conception until after death. Generally, stem cells are classified as: adult, fetal or embryonic stem cells. More recently, umbilical cord blood stem cells, sometimes called 'neonatal' stem cells, have been added as a separate category.

Each stem cell has a unique ability to differentiate into numerous cell types dependent on its potency. Only zygotes are considered totipotent cells, since they are the only cells, which give rise to both every cell type of the embryo and the trophoblast of the placenta. This ability distinguishes them from pluripotent stem cells, which are able to differentiate into all cell types of the embryo except the trophoblast. These cells are usually referred to as embryonic stem cells. In contrast, the differentiation potential of multipotent stem cells, which are usually adult stem cells, is limited to a subset of cell types. Another accepted nomenclature of different stem cell types is related to their tissue specificity. For example, adult stem cells of the nervous system are known as neural stem cells (NSC) whereas blood-forming hematopoietic stem cells (HSC) circulate in the blood.

The potential of stem cells to generate various cell types has emerged great interest for pre-clinical and clinical investigations to cure and repair injured tissues. In the last decade, extensive progress has been made on characterization, isolation, in vitro differentiation and transplantation of multiple stem cell types into various pre-clinical animal disease models. Replacement of lost endogenous cells either by transplantation or by recruitment of resident stem cells is the main goal of stem cell research. Investigations focus on cell replacement strategies for degenerative disorders such as Alzheimer´s or Parkinson´s disease, to cure diabetes with pancreatic cells differentiated from stem cells, to replace damaged cells after myocardial infarction or to replenish immune deficiencies. It is further suggested that stem cells could offer several other approaches for tissue repair as they might facilitate regeneration by providing trophic factors or a permissive substrate for regeneration of endogenous cells.

1. Adult stem cells

In some organs, such as the bone marrow, hair follicle, epidermis, gut and brain, stem cells reside throughout lifetime. In other organs, stem cells divide only after stimulation, usually in response to stress. It has usually been assumed that adult stem cells are multipotent, that is, only capable of developing into cell types of the associated organ or area of the body. Over the past six years, studies have suggested that some adult stem cells have greater plasticity than previously believed, especially stem cells found in the bone marrow (haematopoietic stem cells, mesenchymal stem cells and endothelial progenitor cells) (Verfaillie, Pera and Lansdorp). Haematopoietic stem cells (HSC) are the best characterized adult stem cells.[18, 19]

HSC reside in the adult bone marrow, which further contains different haematopoietic and non-haematopoietic cells. Osteoblasts (mesenchymal cells producing bone matrix), which are localized close to the bone, are known to form and maintain the function of the HSC niche.[20,21,22] HSC can be directly isolated from bone marrow but also after peripheral blood mobilization and from human umbilical cord blood which are successfully used for reconstitution of the haematopoietic system after bone marrow ablation.

In addition to HSC, another stem cell population resides in the bone marrow, named mesenchymal stem cells (MSC). These cells give rise to bone, cartilage, adipose and fibrous tissue.[23] It has been suggested that MSC are in close association with HSC to retain their quiescence[24] and maintenance.[25] However, purification of a homogenous MSC population from bone marrow is lacking due to an incomplete cell marker profile. In contrast, crypt base columnar cells were recently characterized as gut epithelial stem cells by an exclusive expression of Lgr5 (leucine-rich-repeat-containing G-protein-

coupled receptor 5, also known as Gpr49). These cells self-renew and give rise to differentiated cells that constantly repopulate the villi.[26]

Another stem cell source is the bulge of a hair follicle where multipotent stem cells differentiate to all epithelial cells within the hair follicle[27] (Morris et al., 2004) and contribute to wound repair in the epidermis.[28] Interestingly, transplanted hair follicle stem cells are able to generate hair follicles, hair and skin epidermis[29]. These findings provide potential for the treatment of hair loss and other disorders of hair and skin.

The existence of neural stem cells in the adult mammalian brain is well established for two different regions: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus. In the SVZ, slowly dividing, radial glia-like cells have been identified as primary neural stem cells. Once activated, these cells generate rapidly dividing transient amplifying precursor cells, which subsequently give rise to neuroblasts that migrate to the olfactory bulb (OB).[30] In the OB, neuroblasts primarily differentiate into GABAergic and dopaminergic interneurons. NSC are also found in the SGZ generating actively self-renewing progenitors and neuroblasts, which mainly differentiate into local neurons. Although NSC have been isolated from other brain regions, active neurogenesis seems to be restricted to SVZ and SGZ in the adult mammalian brain. NSC are the most promising stem cells for clinical applications in neurodegenerative diseases as they can easily give rise to mature neurons and oligodendrocytes.[30]

Adult stem cells have one enormous advantage over stem cells from most other sources: they can be harvested from the patient, ruling out the possibility of immune rejection after transplantation. Immune rejection occurs when the recipient's body fails to accept a transplanted tissue or organ because it is recognised as foreign, and consequently attempts to destroy it. It is the most serious problem faced in surgery involving organ or tissue transplants. Because adult stem cells can be used for autologous transplantation, which refers to a graft in which the donor and recipient area are in the same individual, immunorejection can be avoided. Another advantage of adult stem cells is their limited ability to proliferate, which would reduce the risk of malignancy in therapeutic use.[31] Instead of isolating/culturing/replacing adult stem cells, it has been suggested that adult stem cells present in the body could be triggered to migrate to and regenerate the damaged body-part. This would give us the capacity to re-grow our own tissues and organs, just like zebra fish can re-grow entire limbs and organs (Lanza and Rosenthal). Much research, mainly on the roles played by chemical signals that lead stem cells to damaged body parts, is still required to reach this goal.[31]

2. Neonatal stem cells from the umbilical cord blood

Of all adult stem cells that have been identified, hematopoietic stem cells are the most versatile, and most easy to obtain. Hematological malignancies often require the transplantation of hematopoietic stem cells, which can be isolated from bone marrow, from blood after peripheral blood mobilization or from human umbilical cord blood (hUCB). Umbilical cord blood (UCB) is a rich source of hematopoietic stem cells. UCB stem cells are sometimes categorized as adult stem cells. Others refer to them as fetal cells. More recently, they have been categorized as 'neonatal stem cells'. The first successful transplantation of UCB stem cells was reported by Gluckman and Boxmeyer in 1989, for the treatment of a patient with Fanconi anemia, an inherited form of anemia which leads to bone marrow failure[32]. Up to now, cord blood has emerged as an accepted alternative source of HSC for transplantation in patients.[32]

As suitable HLA (human leukocyte antigen) matched related donors are unavailable for many patients, cord blood from unrelated donors have been increasingly used as an alternative stem cell source for adult patients.[33,34] A lower risk for acute and chronic graft-versus-host-disease (GVHD) despite major HLA disparity compared to bone marrow transplants, the immediate availability and the risk-free donation are further advantages of umbilical cord blood. Unfortunately, it is difficult to receive a single cord blood unit of satisfactory nucleated cell dose for adult patients. In order to overcome that limited number of cells, double cord blood transplantation from different donors has been recognized as one of the most attractive strategies.[35] Another approach to get a sufficient cell number for transplantation is the ex vivo expansion of cord blood cells.[36] In addition to HSC, mesenchymal stem

cells (MSC) can be isolated from umbilical cord blood and expanded as adherent, fibroblastic-like cells in vitro, which is similar in characteristics to MSC populations from bone marrow. MSC are defined as multipotent cells, which can be differentiated into diverse cell types, e.g. osteocytes, chondrocytes and adipocytes.[37, 38] On the other hand, ectodermal and endodermal differentiation potential of MSC from both bone marrow and umbilical cord blood is controversially discussed since different in vitro differentiation protocols have been described to induce marker expression but in vivo confirmation is still lacking. Instead of cell replacement, MSC are thought to provide trophic support, which might influence the recruitment of endogenous stem cells to the injured tissue. Moreover, MSC are known to have immunomodulatory properties as they can inhibit T-cell proliferation in vitro and in vivo.[39] In animal models of clinical relevant diseases, MSC transplantation was shown to have beneficial effects. Interestingly, it has been demonstrated that MSC can decrease oligodendrocyte apoptosis, demyelination and clinical signs after transplantation into an animal model of multiple sclerosis.[40] In a model of amyotrophic lateral sclerosis (ALS), MSC transplantation has been shown to reduce astrogliosis and microglial activation while increasing motor neuron survival and motor performance. Rather little is known about the involved mechanisms but the promising results make MSC attractive for further investigations.[41]

3. Fetal stem cells

In 1998, John Gearhart and his team at the Johns Hopkins University School of Medicine was the first to establish pluripotent stem cells from human fetuses or post-implantation embryos.[42] His team isolated and cultured primordial germ cells (precursors of eggs and sperm) from the gonadal ridges and mesenteries of 5 to 9 week fetuses obtained by therapeutic abortion. The embryonic germ (EG) cells thus obtained have been shown to give rise to cell types of the three germ layers, and can thus be called pluripotent. EG cells represent important in vitro models for cells and developmental biology.[43] However, because pregnancy terminations happen at various times EG cells can be difficult to harvest. There is only a limited time span during which EG cells can be obtained - within the first 8 to 9 weeks after conception. Moreover, EG cells have limited proliferation capacity. Despite these disadvantages, research results suggest EG cells could be therapeutically useful. Human EG cell derivatives have lead to regenerative repair when implanted into rat brains and spinal cords, which offers hope for treatments for neurodegenerative diseases, such as Parkinson's disease.[44] Apart from primordial germ cells, two other sources of fetal stem cells have been investigated: trophoblast stem cells and fetal tissue stem cells.[45] Stem cells derived from human fetal tissue have shown long-term promise in treating strokes in rats.[46]

4. Human Embryonic stem cells (hES)

hES are pluripotent cells derived from the inner cell mass from mammalian blastocyts or from germ cells which can be differentiated into clinically relevant cell types of ectoderm, mesoderm and endoderm in vitro. Further, ESC can be cultured under defined conditions on a large-scale while they maintain their broad differentiation capacity. These features appear to be ideal for clinical cell replacement approaches and regenerative medicine.

Injection of undifferentiated ESC into immunodeficient mice results in growth of teratomas (non-malignant tumours), which contain cell types of all three germ layers, demonstrating their pluripotent nature (Verfaillie, Pera and Lansdorp). Unfortunately, teratocarcinoma formation, which was observed after transplantation of ESC in different mouse models, limits the clinical translation. Tumor formation is supposed to arise by direct transformation of the transplanted ESC followed by uncontrolled proliferation.[47] Currently, it is believed that a pre-differentiation into defined phenotypes and a purification of progenitor cells would probably obviate teratoma formation.

Many studies also have demonstrated the differentiation potential of hES cells in vitro. For instance, hES cells have been shown to give rise to neural progenitors,[48] to insulin-producing cells[49] and cardiomyocites,[50] and endothelial cells.[51] Recent findings suggest that it is also possible to generate in vitro germ cells from hES cells in a Petri dish.[52] If it can be demonstrated that these gamete-forming cells can become mature and are capable of functioning in fertilization and subsequent embryonic development, this would have enormous potential

for infertility treatment, as well as for the shortage of eggs in therapeutic cloning.[53]

A public debate has emerged focusing on the ethical problems associated with the destruction of the embryo during harvesting of hES. Therefore, alternative methods of establishing pluripotent stem cells that do not interfere with the developmental potential of embryos are studied extensively. Interestingly in this regard, hES can be established without any reduction of the developmental capacity of the embryo with a single cell embryo biopsy, which could possibly circumvent the ethical concerns.[54]

Why choose Cord Blood Stem Cells? (Transplantation for hematological diseases)

The increasing interest in umbilical cord blood after its involvements in hematological clinical applications in the past couple of decades focused efforts on analyzing and characterizing the constituents of umbilical cord blood. Beside the blood cells including erythrocytes, leukocytes and thrombocytes, the umbilical cord blood was found to contain different populations of stem cells, a unique feature not shared with peripheral blood. Scientists and researchers have characterized the following stem cell populations from umbilical cord blood; hematopoietic stem cells (HSCs), multipotent non-hematopoietic stem cells and mesenchymal stem cells (MSCs).

Cord blood transplantation in adults was initially hampered by the low-cell dose and high rates of infection.[55] Two advances have improved these results. First, the use of double cord blood transplants has increased the cell dose administered to patients, allowing blood counts to return more rapidly[56]. Second, non-myeloablative or reduced intensity transplants utilize chemotherapy drugs that are better tolerated and safer, particularly for older patients. These changes have improved survival to 40–60% for adult patients with high-risk leukemia.[57]

Umbilical cord blood has been shown to contain a population of hematopoietic stem cells (HSCs) at different stages of hematopoietic commitment characterized by their differential expression of hematopoietic antigens CD133, CD34 and CD45 according to a previously described model.[58] It has been shown that cord blood hematopoietic stem cells can be selectively induced into specific hematopoietic lineages in-vitro including erythroid, megakaryocytic and monocytic lineages.[59]

There has been great debate on the stem cell source of choice for research and clinical applications. Embryonic stem cells, the least committed stem cells, have been shown to have high proliferation and extensive differentiation capacities, which make them a powerful research platform for studying differentiation pathways and lineage commitment of stem cells.[60,61] Nevertheless, when considering potential clinical applications, embryonic stem cells have shown some major limitations. Embryonic stem cells have high tumorigenic characteristics, which might limit and delay any potential clinical use[62]. Further to this, embryonic stem cells often lack the proper imprinting patterns and regulation of certain genes, which might lead to spontaneous uncontrolled differentiation and developmental abnormalities.[63] It has also been found that embryonic stem cells increaseb their immunogenicity by gaining human leukocyte antigens (HLA) during and after differentiation, which might increase the risk of rejection.[64-66] Nevertheless, the ability to generate pluripotent stem cells from the patient's own cells (iPS cells) should offer an alternative to bypass this limitation. Moreover, the isolation of embryonic stem cells from the inner cell mass of the blastocyst involves the destruction of an embryo which itself creates ethical, religious and political problems.[64-66]

Advantages of Umbilical Cord Blood Transplantation

Umbilical cord blood stem cells also show a number of advantages over adult stem cells sources like bone marrow. The collection of umbilical cord blood stem cells is a safe and non-invasive procedure, unlike the collection of adult stem cells from bone marrow[67]. Moreover, umbilical cord blood stem cells occupy an intermediate age stage between embryonic stem cells and adult stem cells, which leads to higher proliferating potential and longer telomeres than other adult stem cells.[68-70]

Another advantage of umbilical cord blood is the ability to store and cryopreserve cord blood units in cord blood banks for future use. This feature provides clinicians and patients with an immediate and abundant supply of cord blood units for transplantation. It also increases the chance of finding the right HLA-matched units for patients requiring

allogeneic transplantation. Many cord blood banks have been established in the U.K, France and many other countries worldwide for such purposes.[71-73]

Adult stem cell plasticity, however, has been called into question, in part because, (i) most of the studies that have demonstrated adult stem cell plasticity have not been confirmed by independent research teams; (ii) because of the low frequency at with which apparent cell transdifferentiation occurs, and (iii) because most studies cannot prove that the plasticity is the result of a single stem cell that differentiates into more than one functionally characterized lineages.

In an effort to prove the plasticity of umbilical cord blood derived stem cells in relation to other stem cell populations, in vitro and in vivo differentiation protocols have been performed. UCB have been successfully differentiated into cells from all three germ layers. Mesodermal cell types, such as osteoblasts, chondrocytes, and adipocytes, are most commonly used to identify a stem cell's ability to differentiate. However, differentiation into cells of the ectodermal or endodermal layer tends to be more difficult. Umbilical cord blood has added advantages over other sources of stem cells, highlighting its potential as a promising therapeutic tool for many diseases and disorders for which the current form of treatment is inadequate.[71-73]

Cord blood banks and networks

Worldwide, efforts are being undertaken to collect UCB cells and store them in freezers for later use in transplantation. The first cord blood bank was established in New York (New York Blood Center, NYBC) by Dr Pablo Rubinstein[74] (National Cord Blood Program). Since then, large-scale UCB-banking has been established worldwide. Cord blood banking programs have since been initiated at several places in United States,[75,76] Europe,[77] Australia[78] and Asia.[79,80] Forty cord blood banks or registries in 24 countries participate in WMDA[81]. To date, more than 100,000 UCB units are registered and available for transplantation in more than 50 banks worldwide and more than 3000 patients, most of which are children, have received UCB stem cells from these banks.[82]

There is a growing consensus among scientists on the great value of UCB stem cells for transplantation. They are easy to obtain and have been shown to be more versatile than other adult stem cells. Kogler and colleagues, for example, identified human adult stem cells from the umbilical cord blood with intrinsic pluripotent differentiation potential.[83]. UCB has several advantages over bone marrow transplantation: the large donor pool, the low incidence of viral infection at birth, the low incidence of graft versus host disease due to the immune immaturity of the newborn (UCB stem cells are less mature than hematopoietic stem cells found in the bone marrow), the increased speed of availability in stem cell banks and the less costly use.[84] One disadvantage is that the number of UCB stem cells in one umbilical cord is too small to treat an adult. However, research is being pursued to overcome this problem and adults have been successfully treated with UCB stem cells.[85]

To enable an HLA type-based search of donors from bone marrow and peripheral blood stem cell donor registries across the world, Bone Marrow Donors Worldwide (BMDW) was established by EBMT.[81] BMDW released its first listing of 156 000 donors in February 1989. Currently, more than 9 million potential donors are listed. Large national registries in the USA, e.g. the National Marrow Donor Program (www.nmdp.org) and the Caitlin Raymond International Registry (www.crir.org), also participate in BMDW. Although BMDW was first established to allow for international searches of tissue typed adult donors, cord blood units are also currently listed. At present, 37 cord blood registries in 21 countries (with a total of 172 550-cord blood units) participate in BMDW (www.bmdw.org/Database/Donors.htm, as of July 2004).

Netcord, founded in May 1998, is an international non-profit joint effort of leading cord blood banks which has issued statutes and guide-lines with the primary aim of improving the quality of cord blood transplants for clinical cell therapy on the international level,[86] NETCORD and FAHCT, 2001) (www.unmc.edu/Community/fahct). To enable efficient cord blood unit data exchange and allocation, the Netcord inventory is available for searches in a virtual office via the internet (office. de.netcord.org). In addition, cord blood banks in Asia are now associated under the name of Asiacord.[79] To enable coordinated management of complicated

international hematopoietic stem cell donor search processes, search activities in each country have been centralized to national hubs.

Private, public or hybrid banking?

UCB banks can be private or public. Private UCB banks store UCB for the family's own use. Parents have to pay for storage of the UCB of their child. The idea is that should the child or another family member at some point in his/her life need a haematopoietic stem cell transplant, these cells will be immediately available, and will (very likely) be an HLA-match. Public UCB banks collect UCB after consent of the mother. Storage is free, but the UCB is intended for any patient in need of a UCB transplant. It is not reserved for the family's private use. Doctors all over the world search the National Marrow Donor Program Registry of donors and cord blood units to find a match for their patients who need a transplant. Since hematopoietic stem cells from umbilical cord blood have greater potential as a collective asset than as an individual asset, eligible pregnant women should be encouraged to consider public cord blood donation by their prenatal care providers.

Average volume of cord blood for banking

Cord blood volume obtained from the umbilical vein during collection may vary between 0 and 255 ml depending on the collection technique and mode of delivery.[87] Banks routinely use a cut-off limit of collected cord blood, e.g. 40ml, to increase the cell yield available for banking.[87] Depending on the selected cut-off limit, an average collected cord blood volume reported has been 68-107ml.[87,88]

Collected total cell amount naturally also varies according to the collected volume. Total nucleated cell counts, such as 102-169x10^7/unit, have been reported[87,88], which may reflect the actual cut-off limits set for collected volume and nucleated cell concentrations analysed by the individual banks.

Lingering Challenges to stem cell transplantation

Challenges for hES cell research

Science of pluripotent hES cells is still in its infancy. Many technical issues remain to be solved.[89] More research is needed into the self-renewing capacity of hES cells, and into means to ensure stability of genotype, epigenetic status, and phenotypic properties of hES cells. hES cells need to be generated in pure form and in sufficient numbers to be therapeutically useful. Another challenge is to direct the differentiation of hES cells down a particular pathway to generate the desired cells that are restricted to specific developmental fates. In addition, a better understanding is required of what stem cell type to supply for treating a particular pathology, and how to deliver it. For instance, by simply injecting hES cells into the damaged body part, or by first coaxing them into progenitor cells or fully differentiated cells. Transplanted hES cell progeny may not function normally in organs and might retain tumorigenic potential, a characteristic of hES cells. As said before, the avoidance of immunological rejection remains one of the biggest challenges. There are numerous unanswered questions as to the control of ES cell growth and differentiation. ES cells have the potential to be tumorigenic, growing into teratomas and teratocarcinomas when injected into mice. Research is being done on this worldwide and progress is being made.[90] Recent research shows there may be infectious and other risks, such as occurred with BSE, of transplanting such tissue back to people, when it is grown on foreign culture material.[91]

Challenges for UCB cell research

Despite the undisputed role of UCB as an abundant and readily available alternative source of stem cell, the relatively low numbers of stem- and progenitor cells in a single unit limit the use of UCB in HCT. Given the low cell numbers, prime targets for cord blood transplantation (CBT) are pediatric group of patients. According to the Center for International Blood and Marrow Transplant Research (CIBMTR), UCB accounts for more than 40% of allogeneic unrelated HCT in children, while the corresponding number in adults is only approximately 10%.[92] There of apparent link between infusion of low cell numbers and delayed immune reconstitution, which in turn increases the risk of early transplant-related mortality. Subsequently, the main challenge is to overcome the cell-dose limitation.[93]

Simplified, the more cells transplanted, the faster recovery, the better outcome. Substantial clinical benefit may be achieved through generation of sufficiently high numbers of progenitors that ensure faster hematopoietic recovery and thus counteract the transplantation-induced neutropenia, while at the

same time providing stem cells for stable long-term engraftment. To make UCB as a donor choice more feasible for adult patients, extensive research has been devoted to find strategies that would improve the numbers, potency, and engraftment capabilities of transplantable HSPCs prior to transplantation.[93]

There is also the potential for transfer of genetically abnormal cells. In addition, clinical results show that the frequency and rate of myeloid and platelet engraftment are slower than that observed with comparably matched bone marrow, leading to the possibility of increased rates of engraftment failure and transplant-related mortality.[94,95] In contrast to bone marrow or peripheral blood progenitor cell transplantation, where it is possible to seek subsequent donations if needed, the unrelated cord blood donor cannot offer a second donation in the event of marrow failure or relapse of the disease.[94,95]

As the transplant recipient is at a significant risk for morbidity before engraftment, speedy recovery of neutrophils and platelets is essential. Engraftment can be evaluated by assessing the degree of chimerism i.e., the proportion of donor-derived myeloid and lymphoid cells versus those of patient origin.[96] In primary graft failure, engraftment fails to occur and the graft never produces an adequate number of blood cells. In secondary graft failure, blood cells are initially produced but the function of the graft ceases later. RBC recovery may also be delayed after hematopoietic stem cell transplantation.[97]

HLA matching is essential for the success of hematopoietic stem cell transplantation, including minimizing the risk of GVHD.[98] In addition, the direction of the HLA mismatch has recently been suggested to be better tolerated in UCB than in BM transplantation.[100] Importantly, however, a better HLA match has been reported to decrease the TNC dose required to achieve the same level of transplant related mortality in UCB transplantation.[99]

Engraftment has been reported to be slower after UCB than after BM transplantation; in contrast, the risk of acute GVHD is reportedly lower.[101] The risk of chronic GVHD may be similar or slightly reduced in UCB transplantation compared to BM transplantation. As the UCB unit is available, immediately, without the delays of contacting and testing a potential donor, UCB may be a better alternative in emergency situations. On the other hand supporting cells or a new hematopoietic stem cell graft can often be collected from a BM donor if needed, an alternative not available for UCB recipients.[101]

Altogether, survival after UCB transplantation has been reported to be comparable to that after BM transplantation.[100] However, most comparative studies of UCB and BM transplantation have been retrospective, and the patients have not been matched for diagnosis, disease stage, pre-transplant conditioning, the grade of HLA matching, or other factors affecting the outcome of the hematopoietic stem cell transplantation. UCB transplantation results have been analyzed in heterogeneous groups of patients, and the recipients have often had a poor transplant prognosis due to e.g. advanced disease. Incomplete HLA matches have had to be accepted, and the TNC dose/kg patient weight has varied widely even within the studies. Thus comparative studies of CB and BM transplantation are scarce.[100]

In recent studies of one-unit transplantation, the median TNC count of the transplanted UCB units has been approximately 90-160 x 10^7. However, the increasing proportion of adult UCB recipients has led to rising requirements for CB unit HPCs and thus, TNCs. The minimum HPC dose required for successful transplantation also depends on the degree of HLA mismatching.[104] Target TNC doses of 3.0x10^7/kg for HLA matched units and 4.0x10^7/kg for HLA-mismatched units have been applied[102]. To overcome HLA mismatches at 1-2 loci, a cryopreserved TNC dose of at least 2.5-5.0x10^7/kg patient weight has been reported to be required to minimize UCB transplant-related mortality[99]. Thus, both the available TNC does and the degree of HLA matching have to be considered when selecting the best UCB unit for each patient.

The transplantation of two UCB units to increase the TNC dose has yielded promising results in adults.[99,102] However, the probability of finding two UCB units both HLA-mismatches have had to be accepted. The risk of acute GVHD may be increased after the transplantation of two UCB units.[103] The CD34+ cell dose[104] and the CFU dose[105] have been suggested to be better determinants of neutrophil and platelet engraftment than the TNC dose. In some studies,

neither the TNC dose nor the CD34+ cell or the CFU-GM doses have correlated with engraftment.[106] Due to problems with the interlaboratory standardization of CD34+ cell and CFU enumeration, the TNC count is still applied in international registries for the selection of UCB units for transplantation. Finally, cord blood collection, storage, and transplantation raises numerous financial, ethical, and regulatory issues for health care providers and society.

Safety Aspects of Cord Blood Banking

Once collected, cord blood units are labelled and shipped to the bank, where they undergo safety testing, human leukocyte antigen typing, and cryopreservation. Public banks generally follow procedures in accordance with established standards.[106] Procedures for transfer of cord blood units from birth hospital to private cord blood banks are less well controlled and defined. There is currently no requirement for registration or regulation of cord blood collection centres, banks, or transplant centres in Canada. Testing cord blood and maternal blood for infectious agents (HIV, cytomegalovirus, human lymphotropic virus, hepatitis viruses, and syphilis) is required by public cord blood banks. Cord blood units are initially placed in quarantine until infectious testing is completed. If new units test negative for infectious diseases, they are placed in long-term storage banks. Public banks also obtain detailed maternal and family history of genetic diseases, travel to countries with high rates of transmissible infections, and other high-risk behavior regarding intravenous drug use and sexual behavior. Cord blood unit screening is the same as that used by the Canadian Red Cross for blood donors.[106]

CONCLUSION

The scientific community has access to a widely varied population of stem cells with which to investigate the biology and potential application of the stem cell. Undoubtedly, certain cell types are more suited for use in different situations. Human umbilical cord blood is probably the largest, but under-utilized source of stem cells with the yearly global birth rate of 200 million per year.[66] Cord blood non-hematopoietic multipotent stem cells, which demonstrated high potential for neural differentiation, are easily accessible, immunologically naive and are free from ethical controversies associated with other sources of stem cells. These added advantages made umbilical cord blood stem cells a potential candidate for disorders and clinical applications of those whose current mode of therapy is inadequate. One disadvantage is that the number of UCB stem cells in one umbilical cord is too small to treat an adult. However, in order to assure potentially effective treatments and the banking of autologous cord blood in private cord blood banks is based on the hope that it may, at some point in the future, be of therapeutic benefit in treating or curing any form of chronic or degenerative disease in its donor or in others. At present, this is entirely speculative. Applications of umbilical cord blood stem cells, more research should be directed toward understanding the molecular properties of umbilical cord blood. This requires the development of effective purification and enrichment strategies of such cells to allow accurate analysis of the molecular mechanisms.

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The high Percentages of Anti-thyroid Antibodies Positive SLE Patients at Sheikh Zayed Hospital, Lahore (Pakistan)

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ABSTRACT

BACKGROUND & OBJECTIVES: Systemic lupus erythmatosus (SLE) is an autoimmune disease and more than 100 auto antibodies have been detected in SLE. The present study was designed to determine the presence of anti-thyroid antibodies (ATA) in SLE patients. **METHODS:** It was a descriptive study and 42-SLE patients positive for anti-nuclear antibodies (ANA) and or anti-ds DNA (ds-DNA) antibodies were selected from Department of Rheumatology, Sheikh Zayed Hospital Lahore. Blood sample was collected and ATA was determined by indirect immunofluorescence technique. **RESULTS:** Thirty-nine (39) (92.9%) and 32 (76.2%) patients had ANA and ds-DNA antibodies respectively. On comparison, it was not statistically significant. Twenty-three (23) (54.76%) subjects had ATA and on comparison, it was not statistically significant. All the positive patients for ATA were females. **CONCLUSION:** Sensitivity of ANA and ds-DNA positive suspected SLE subjects to have ATA in their serum was 74%. About 55% of SLE patients were positive for ATA.

Key words: Systemic lupus erythematosus, anti-thyroid Antibodies, Immunofluorescence

الملخص

المقدمة والأهداف: تعتبر الذئبة الحمراء أحد أمراض المناعة الذاتية، وهنالك أكثر من ١٠٠ من الأجسام المضادة الذاتية تم اكتشافها في الذئبة الحمراء. هذه الدراسة قد تم تصميمها لتحديد وجود اجسام مضادة للغدة الدرقية في مرضي الذئبة الحمراء. **منهج الدراسة:** دراسة وصفية تم فيها دراسة ٤٢ مريض ايجابي للأضداد النووية (ANA) و / أو مضادات الدي ان اي (DS-DNA) تم اختيارهم من قسم لأمراض الروماتيزمية بمستشفى الشيخ زايد بلاهور. تم فحص وجود اجسام مضادة للغدة الدرقية في الدم بواسطة تقنية الومضان المناعي الغير مباشر. **النتائج:** ٣٩ مريض (٩٢,٩٪) كان ايجابي للأضداد النووية (ANA)، و٣٢ مريض (٧٦,٢٪) كان ايجابي لمضادات الدي ان اي (DS-DNA). وعلى سبيل المقارنة، لم يكن الفرق يعتد به إحصائيا. ٢٣ مريض (٥٤,٧٦٪) كان ايجابيون لوجود اجسام مضادة للغدة الدرقية (ANA) وعلى سبيل المقارنة، لم يكن ذات دلالة إحصائية. جميع المرضى الإيجابيون لوجود اجسام مضادة للغدة الدرقية (ANA) كانوا إناث. **الخلاصة:** حساسية وجود اجسام مضادة للغدة الدرقية (ATA) لدي المرضي الايجابيين للأضداد النووية (ANA) و لمضادات الدي ان اي (DS-DNA) ٧٤٪ . و حوالي ٥٥٪ من مرضى الذئبة الحمراء كانوا ايجابيون النتائج للأضداد النووية (ANA)

INTRODUCTION

Autoimmune diseases occur when physiological tolerance of self-antigens is lost and thereafter, human body cannot discriminate between self and non-self-tissue. Multiple factors such as environment, heredity, viruses, drugs, etc. may contribute towards an autoimmune disease.[1] Autoimmune diseases are categorized into systemic and organ specific diseases and production of auto-antibodies is the hallmark of these diseases[2] where auto-antibodies results in variety of pathologic manifestations.[3]

Systemic lupus erthematosus (SLE) is a systemic multi-organ autoimmune disorder, where microvascular inflammation is one of the characteristic features.[4] Like other autoimmune disorders, exact cause of SLE is not known, but multiple factors such as racial, genetic, hormonal, and environmental are associated with it.[5, 6]

The American College of Rheumatology, in 1982, established criteria to diagnose SLE and in 1997 they revised it. In 2012 the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria of 1997. They classified a person as having SLE in the presence of biopsy-proven lupus nephritis with ANA or anti-dsDNA antibodies or if 4 of the diagnostic criteria, including at least one clinical and one immunologic criterion, have been satisfied.[7]

In SLE, auto antibodies contribute towards pathogenesis of disease manifestations. Systemic lupus erythematosus (SLE) patients show defective early B cell tolerance checkpoints and therefore

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accumulate self-reactive and polyreactive antibodies.[8] Antinuclear antibodies (ANA) are found in nearly all the active SLE patients but antibodies to native ds-DNA have been suggested as the specific marker for diagnosis of SLE.[9]

The annual incidence of SLE averages 5 cases per 100,000 population. The Centers for Disease Control and Prevention (CDC) estimates a range between 1.8 and 7.6 per 100,000 persons per year in the continental United States.[10] The reported prevalence ranges from 52 cases per 100,000 population.[11] It is consistent with the 2005 CDC estimates of 161,000 definite cases and 322,000 probable or definite SLE cases in the United States to estimates as high as 1:1000.[10]

The Lupus Foundation of American estimates prevalence to be up to 1.5 million cases, which likely reflects inclusion of milder forms of this disease. According to a 2008 report from the National Arthritis Data Working Group, approximately 250,000 Americans have definite SLE.[12]

In SLE, there is high level of interferon secretion, that results in an aberrant expression of major histocompatibility complex antigen by thyrocytes which provokes an autoimmune response and production of antithyroid antibodies.[13]

In SLE, more than 100 auto antibodies have been detected.[14] Antibodies against thyroid antigens have been documented in a number of non-organ-specific rheumatological disorders such as SLE.[15] Therefore, in SLE anti-thyroid activity by auto antibodies may result in thyroid disorders.[16] Autoimmune thyroid disorders are characterized by anti-thyroglobulin (ATA) and anti-thyroid peroxidase autoantibodies.[17] These two antibodies are collectively named as anti-thyroid antibodies (ATA).[18]

In SLE, prevalence of autoimmune thyroid disorders was documented between 3.9%–24% and the frequency of anti-thyroid antibodies was between 11-51%.[19] Another study suggested that 14% anti-thyroid antibodies are present in SLE.[20]

Therefore a study was designed to determine the percentage of anti-thyroid antibodies positive SLE patients visiting Sheikh Zayed Hospital Lahore Pakistan. For the detection of anti-thyroid antibodies different laboratory techniques have been used, e.g. ELISA and indirect Immunofluerescence (IIF). IIF method is more reliable and specific compared to ELISA[21], therefore IIF technique was opted for this study.

Materials and Methods

Samples:

Blood samples of 42 SLE patients from the Department of Immunology & Rheumatology Sheikh Zayed Hospital, Lahore were collected. These patients were diagnosed according to the criteria of American College of Rheumatology. These SLE patients were positive for anti-nuclear (ANA) antibody or anti double stranded DNA antibody (anti-ds DNA).

Determination of ATA:

The anti-thyroid antibodies were determined in the Department of Immunology, University of Health Sciences (UHS) Lahore by the indirect immunofluorescence technique by using slides coated with thyroid tissue (Orgentec Company Limited Germany).

The antibodies of the diluted patient samples and controls were allowed to react specifically with the antigens of the tissue sections immobilized on the slides. After an incubation period of 30 minutes at room temperature(RT) (15-30°C), unbound serum components were removed by a wash step. The bound antibodies were allowed to react specifically with anti-human IgG conjugated to Fluorescein-isothiocyanat (FITC). After an incubation period of 30 minutes at RT (15-30°C) excessive conjugate was separated from the solid-phase immune complexes a wash step. Stained slides were read using a fluorescence microscope(Olympus CX41). The study was approved by the Ethical Review Committee and Advanced Study and Research Board of UHS and Sheikh Zayed Hospital Lahore. Written informed consent of each participant was obtained before collecting their blood sample.

Data Analysis: The data was entered and analysed using Predictive Analytics Software (PASW) 18.0. Mean±SD for quantitative variables, while frequencies, percentages and graphs were given for qualitative variables. A p-value of <0.05 was considered as statistically significant. OpenEpi, Version 3 was used to calculate sensitivity of different parameters.

RESULTS

Among 42 diagnosed SLE patients, there were 41 (98%) females and only 1 (2%) male. The mean ± SD of age of SLE patients was 27±7.1 years (range 15–45). Thirty nine (93%) SLE patients were positive for ANA while 03(7%) were negative for these antibodies. Among the studied population, 32 (76%) SLE patients were positive for anti-ds DNA antibody while 10(24%) patients were negative for this antibody. Anti-thyroid antibodies were present in 23(54.76%) patients, while 19(45%) patients were negative for this antibody. Number, percentage and comparison of ATA positive and ATA negative with ANA and anti-dsDNA is presented in Table 1. The presenting complaints of the studied population are presented in Table 2.

DISCUSSION

The current study included 42 SLE patients that comprised of 41 females (98%) and 1 (2%) male patient and they were between 15-45 years with the mean age of 27 years. Regarding the percentage of gender and mean age of the subjects, current study is in agreement with the study of Konho et al., (1989)[22] who also included 98% SLE females and their mean age was 27.4 years. Inclusion of more females in the current study could entail the higher percentage of ATA in this study as the prevalence and incidence of thyroid disorders is influenced primarily by gender.[23]

In the current study among 42 SLE patients, 39 (93%) patients were positive for ANA. These results are in agreement with the findings of Gibson et al.[24] because they also reported presence of ANA in 95% of SLE patients. The current study is also in agreement with the study of Gill et al[25] because they documented that more than 99% of patients with systemic lupus erythematosus have an elevated ANA. However, the current study is not in agreement with the study of Tektonidou et al[26] who reported ANA in 35% of SLE patients. The probable reason for this discrepancy could be due to the larger number of patients included in their study (168) as compared to the current study which included 42 patients.

In the current study 23 (55%) of SLE patients were positive for ATA. The current study is in agreement with the study of El-saadanya et al[27] who reported that Anti-TPO abs and anti-TG abs were more frequently detected in SLE 85% and 55% respectively. Magaro et al[28] also reported antithyroid antibodies in 45% of their SLE patients. The small difference between the percentages of ATA in both the studies could be due to the methodology used for the detection of these antibodies because in the current study IIF technique was used that is more specific as compared to ELISA technique which was used in the other studies. The study of Pyne et al[20] is not in agreement with the current study as they documented anti-thyroid antibodies in 14% of SLE subjects.

In the current study, among 42 SLE patients, 19 (49%) patients had proteinuria which is in agreement with the study of Akbarian et al[29] because they documented presence of proteinuria in up to 55% of SLE patients. However, current study is not in agreement with the study of Christopher et al[30] bezcause they documented presence of proteinuria in 77% of SLE patients. The difference in the percentages of the subjects with proteinuria in two studies could be due to the differences in the stages of SLE patients included in these studies. In the current study, 28 SLE patients (67%) had complaints of arthritis that is in agreement with Cervera et al[31] as they documented arthritis in 71% of SLE patients.

In the current study, 15 SLE patients (36%) had malar rash and 9 (21.4%) patients had oral ulcer. These findings are in agreement with the study of Boddaert et al., (2004)[32] who documented malar rash as

Table 1: Number, percentage and composition of ATA positive and ATA negative with ANA and anti-dsDNA

		ATA Positive	ATA Negative	Total	p value
ANA	Positive	21 (91.3%)	18 (94.7%)	39 (92.9%)	0.667
	Negative	2 (8.7%)	1 (5.3%)	3 (7.1%)	
Anti-ds DNA	Positive	18 (73.7%)	14 (73.7%)	32 (76.2%)	0.729
	Negative	5 (21.7%	5 (26.3%)	10 (23.8%)	

Table 2: Number, percentage and comparison of presenting complaints of ATA posivite and negative subject

ATA Positive	Presenting complaint	Age Range				p value
		15-30		31-45		
		Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	
	Oral Ulcer	3 (18.8)	13 (81.2)	3 (42.9)	4 (57.1)	0.318
	Arthritis	7 (43.8)	9 (56.2)	5 (71.4)	2 (28.6)	0.371
	Malar Rash	7 (43.8)	9 (56.2)	4 (57.1)	3 (42.9)	0.667
	Proteinuria	8 (50)	8 (50)	4 (60)	3 (40)	0.999
	ANA	14 (87.5)	2 (12.5)	7 (100)	0 (0.0)	0.557
	Anti-ds DNA	12 (75)	4 (25)	6 (85.7)	1 (14.3)	0.550
ATA Negative	Oral Ulcer	2 (14.3)	12 (85.7)	0 (0)	2 (10.5)	0.999
	Arthritis	11 (78.6)	3 (21.4)	5 (100)	0 (0)	0.530
	Malar Rash	3 (21.4)	11 (78.6)	1 (20)	40(80)	0.999
	Proteinuria	4 (28.6)	10 (71.4)	3 (60)	2 (40)	0.301
	ANA	14 (100)	0 (0.0)	4 (80)	1 (20)	0.263
	Anti-ds DNA	10 (71.4)	4 (28.6)	4 (80)	1 (20)	0.999

31% in their studied population. However, current study is not in agreement with Cervera et al[31] who documented malar rash as 79% in SLE patients.

Conclusion

Anti-thyroid antibodies were detected in high percentage (55%) of SLE patients.

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Recommendation

Level of anti-thyroid and other antibodies should be determined in larger group of different autoimmune disorders.

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Estimation of Height from Measuring Foot, Hand and Head Length in Northern Indian Population

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ABSTRACT

BACKGROUND & OBJECTIVES: Estimation of height from foot length, hand length and head length is important for forensic experts for establishing the identity, for anthropologists regarding data collection and research and for epidemiologists in performing statistical analysis. The aim of the study was to deduce the height from foot length, hand length and head length in North Indian population by conducting a pilot study in medical students of North India

MATERIALS & METHODS: Ethical clearance was taken from college human ethical committee. A total of 194 students both male and female with the age group 19-23 years were analyzed by SPSS software. The foot length, head length, and hand length was correlated with estimation of height by using linear and multiple regression analysis. Results were compared among male and female in similar age group.

RESULTS: It was found that hand and foot length is strongly associated with height whereas head length showed no correlation with the height in both male and females.

CONCLUSION: Hand length and foot are strong predictors for estimating the height of an individual.

Key words: Height, hand length, foot length, head length, anthropometry, identification.

الملخص

المقدمة: تقدير الطول من طول القدم، طول اليد، وطول الرأس مهم جدا بالنسبة لخبراء الطب الشرعي وذلك لتحديد الهوية، ولعلماء الأنثروبولوجيا فيما يتعلق بجمع البيانات والبحوث، ولعلماء الأوبئة لأداء التحليل الإحصائي. **هدف الدراسة:** الاستدلال على طول الجسم بواسطة معرفة طول القدم، طول اليد وطول الرأس في سكان شمال الهند عن طريق إجراء دراسة تجريبية في طلاب الطب من شمال الهند. **منهج الدراسة:** بعد أخذ الموافقة الأخلاقية، تم تحليل قياسات طول القدم واليد والراس لعدد 194 طالب من الذكور والإناث من الفئة العمرية 19-23 عاما بواسطة برنامج SPSS. تم حساب الارتباط بين طول القدم وطول اليد وطول الرأس مع تقدير طول الجسم باستخدام التحليل الخطي والتراجع المتعدد. وتمت مقارنة النتائج بين الذكور والإناث في نفس الفئة العمرية. **النتائج:** لقد وجد ارتباط قوي بين طول اليد وطول القدم مع طول الجسم في حين لم يظهر طول الرأس أي ارتباط مع طول الجسم في كل من الذكور والإناث. **الخلاصة:** لطول اليد والقدم القدرة القوية لتقدير طول الفرد .

INTRODUCTION

All human beings are not identical; they differ in their measurements; even monozygotic twins are different, and this can be attributed to different geographic location, diet and socioeconomic status. Height is an important indicator of nutritional status, body surface area, growth and pulmonary function. It can useful for forensic experts for the identification of unidentified human body. It also facilitates anthropologist for determining the race. Therefore, the estimation of height from different body parts is of utmost importance as height measurement by long bones was done frequently in the past and deduced different formulae for different bones. In the current study, we used hand, foot and head length which can be correlated with living or dead human body for height estimation. Height estimation by long bones was done in the past[1-4]. Attempts had been in the past to estimate height by using foot length[5-7]. All of them stressed upon the importance of morphometric analysis of the human body, especially estimation of height by different methods.

MATERIALS AND METHODS

It was a cross-sectional study by design. A total of 194 (Males=107 and Females=87) asymptomatic, apparently healthy, young adult of age group 19-23 years were selected. The data was collected from

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August 13, 2013 – January 25, 2014. The sample size was calculated using level of precision formula. All of the subjects were students of Government Dental College at Aligarh. Their socioeconomic and nutritional status was not assessed and four parameters were assessed i.e., Height, Foot Length, Hand length, Head length.

Measurements were taken by using standard anthropometric instruments in centimeters to the nearest millimeter according to techniques described. [8] Height of the individual was measured in standing erect anatomical position with standing height measuring instrument. Head length was measured by measuring tape from glabella to inion Foot length was considered as the maximum length between the most prominent posterior point of the heel and the tip of hallux and the tip of the second toe if it is larger than the hallux. Hand length –The distance between the midpoint of the inter styloid line and the tip of the middle finger in extension.[9-10]

OBSERVATION AND RESULTS

The data was analyzed by SPSS software, and the methods were used with linear and multiple regression analysis. The observations were done on 107 male and 87 female students. Correlations were applied to observe the direction of the relationship between various parameters. The results showed that, in males, significant positive correlation was observed between height & hand (r=0.932, p<0.001), height & foot (r=0.896, p<0.001) and between hand & foot (r=0.865, p<0.001). In females, also significant positive correlations were observed between height & hand (r=0.952, p<0.001), height & foot (r=0.920, p<0.001) and between hand & foot(r=0.897, p<0.001). However, in both males and females; head length was not significantly correlated with hand, foot and height (p>0.05). Table 1, 2 and 3 reflects linear regression analysis for observations among males, females and total cases respectively. It clearly reflects that foot and hand length are very good indicators of height as p value<0.001. On the other hand, head length is not significant (p value < 0.05).

Multiple linear regression analysis was also applied separately in males and females to develop a model for predicting height from hand, foot, hand and head length. In males, the three predictor model was able to account for 89.7% of the variance in height, F (3, 106) = 308.83, p<0.001, adjusted R2 = 0.897. Hand and foot were the significant predictors for height (p<0.01) respectively. In females, the three predictor model was able to account for 86.3% of the variance in height, F (3, 86) = 181.72, p<0.001, adjusted R^2 = 0.863. For females also, hand and foot were the significant predictors for height (p<0.01) respectively. However, head length was the non-predictable parameter for height in both males and females (p>0.05) respectively.

Table 4, 5 and 6 reflects multiple regression analysis in which hand and foot length are highly significant (p value<0.001), whereas head length is a poor indicator of height.

Table 1. Estimation of Height from Measuring Foot, Hand and Head Length in Male cases

Parameter	Correlation coefficient (r)	Regression equation	p value
Foot	0.896	Height = -68.409+9.902	<0.001
Hand Length	0.932	Height = -12.076+9.559	<0.001
Head Length	-0.116	Height = 185.238–1.216	0.234

Table 2. Estimation of Height from Measuring Foot, Hand and Head Length in Female cases

Parameter	Correlation coefficient (r)	Regression equation	p value
Foot	0.952	Height = -37.285+8.917	<0.001
Hand Length	0.920	Height = 129.221+6.528	<0.001
Head Length	0.035	Height = 149.769+0.274	0.750

Table 3. Estimation of Height from Measuring Foot, Hand and Head Length in total cases

Parameter	Correlation coefficient (r)	Regression equation	p value
Foot	0.882	Height = 23.054+6.047	<0.001
Hand Length	0.764	Height = 84.985+4.266	<0.001
Head Length	0.088	Height = 141.630+1.013	0.221

Table 4. Multiple Regression Analysis for Estimation of Height from Measuring Foot, Hand and Head Length in Male cases

Parameter	Multiple correlation coefficient (R and R2)	Regression equation	p value
Foot	R= 0.947 R2= 0.897	Height = -46.864 + 6.954 + 6.388 + 0.024	<0.001
Hand Length			<0.001
Head Length			0.942

Table 5. Multiple Regression Analysis for Estimation of Height from Measuring Foot, Hand and Head Length in Female cases

Parameter	Multiple correlation coefficient (R and R2)	Regression equation	p value
Foot	R= 0.947 R2= 0.897	Height = -41.939 + 8.897 + 7.356 + 0.271	<0.001
Hand Length			<0.001
Head Length			0.905

Table 6. Multiple Regression Analysis for Estimation of Height from Measuring Foot, Hand and Head Length in Total cases

Parameter	Multiple correlation coefficient (R and R2)	Regression equation	p value
Foot	R = 0.822 R2 = 0.759	Height = 38.159 + 5.461 + 4.646 - 0.745	<0.001
Hand Length			<0.001
Head Length			0.261

DISCUSSION

The current study predicts height from head, hand and foot length. Results showed height depends on hand and foot length whereas head length has no correlation with the height. Height was estimated from foot/shoe measurements.[11] Whereas ethnic differences were found between foot and height measurements,[12] Singh and Phookan reported that height estimation by foot length measurement gives better results than height estimation by foot width measurement. Ashizawa et al. stressed that the morphometric assessment must be done with the attention to society.[13] Print media was used by Jasuja and Manjula.[14] The study conducted by Singh JP et al. showed that bare foot measurements are the better predictor of height than shoe measurements.[15]

One of the similar research done by Abdel-Malek et al. concluded that, in multiple linear regression analysis, R2 was 0.68 for hand length, which means if one have hand length, the height can be calculated with 68% accuracy.[16] Similarly this study found R^2, for hand, foot and head length were 0.897 among males, and 0.863 among females, that showed that if the hand, foot and head length altogether available, the height can be predicted with 89.7% accuracy in males and 86.3% accuracy in females (Table 4, 5). Hands and feet are quite good indicator of height, these findings of the current study are in alignment wit study conducted by Kewal[17] that the multiple regression equations are more reliable than linear regression equations. Height prediction by head length alone was found to be insignificant and no correlation was found between head length and height in either sexes. This observation was congruous with the findings of Sonali Khanapurkar.[18] Further study is required to confirm.

CONCLUSION

After comparing all the parameters, it was conclude that foot length (r=0.952) is a better indicator of height in females whereas hand length (r=0.932) is the best indicator of height among males. Head length cannot be used to predict the height as no significant correlation has been found between head length and hand length, foot length, height (P>.05). If all the three parameters were taken together, the accuracy increases in both males and females [r= 0.947 (males), r=0.928 (females)]. It is also clear from the observations that the multiple regression analysis is more effective tool for predicting height more accurately than linear regression analysis.

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Medical Professionals KAP of Depressive Disorder in Pakistan.

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ABSTRACT

OBJECTIVES: To explore the level of knowledge, attitude, and practice patterns of of medical professionals about depressive disorder in Pakistan. The study design is Survey Research conducted at Centers of College of Physicians and Surgeons Pakistan (CPSP) from Karachi, Islamabad, Multan, and Peshawar between March to September 2013. **METHODOLOGY:** Two hundred and sixty three post graduate trainees and specialist who have attended the CPSP workshops were included in the study by using purposive sampling technique. To assess their level of knowledge, attitude, and practice of depressive disorder, researcher has developed a questionnaire. **RESULT:** Participants 'ratio for correct answers regarding knowledge of depressive disorder is 47%, while the ratio for incorrect answers is 52% and 1% respondents didn't reply to the asked question. When participants' attitudes were assessed about depressive disorder, most of them were feeling comfortable to work with the patient of depression, at the same time they believed that it is not easy to work with the patient of depression. Majority of participants reported that they tend to prescribed antidepressants and they also assumed that psychotherapy has place in the treatment of depression. Majority of participants reported that they prescribed selective serotonin reuptake inhibitors (SSRIs) while some of them also believed in the combination treatment. Most of the participants reported that they see less than five patients of depression in a week, and they tended to refer their patients to psychiatrists. Moreover, they believed that most of patients with depression report physical complains and most associated physical complain with depression is headache. **CONCLUSION:** Postgraduate trainees and specialists have relatively low level of knowledge about depression but they have relative positive attitudes and performed some desirable practices in their treatment of depression

Key words: Postgraduate Trainees.Knowledge.Attitude. Practice Patterns. Depression.

الملخص

الاهداف: لاستكشاف مستوى المعرفة، والاتجاهات والسلوك لدي المهنيين الطبيين حول الاكتئاب في باكستان. **منهج الدراسة:** دراسة مسحية في مراكز كلية الاطباء والجراحين بباكستان، في مدن كراتشي، إسلام آباد، ملتان، وبيشاور في الفترة من مارس وحتى سبتمبر 2013. شملت الدراسة مئتان ثلاثة وستون من الخريجين المتدربين ومن المتخصصين الذين حضروا ورش العمل بمراكز كلية الاطباء والجراحين بباكستان، وقد تم اختيارهم باستخدام تقنية أخذ العينات الهادفة. لتقييم مستوى المعرفة، والاتجاهات، والسلوك حول الاكتئاب بواسطة استبانة. **النتائج:** نسبة المشاركين الذين حصلوا إجابة صحيحة فيما يتعلق بالمعرفة حول الاكتئاب هي ٪47، في حين أن نسبة الحاصلين إجابة خطأ هي ٪52 و٪1 لم يرد على السؤال المطروح. عند تقييم اتجاهات المشاركين حول الاكتئاب، أفاد معظمهم بأنهم يشعرون بالراحة عند العمل مع مرضي الاكتئاب، وفي نفس الوقت يعتقدون بأنه ليس من السهل التعامل مع مرضي الاكتئاب. أغلبية المشاركين ذكروا أنهم يميلون إلى وصف مضادات الاكتئاب كعلاج وافترضوا أيضا أن العلاج النفسي مهم في علاج الاكتئاب. ايضا أفاد غالبية المشاركون أنهم بأنهم اعطوا مرضاهم مثبطات امتصاص السيروتونين (SSRIs) في حين أن بعض منهم يعتقد أيضا في فعالية العلاج المركب. أغلبية المشاركين افادوا بأنهم يرون أقل من خمسة مرضى اكتئاب اسبوعيا، وأنهم يحولونهم إلى الأخصائيين النفسيين. وعلاوة على ذلك فان معظم المرضى الذين يعانون من الاكتئاب يهم اعراض جسمانية واغلب ما يشتكون من الصداع. **الخلاصة:** الخريجين المتدربين و المتخصصين لديهم مستوى منخفض نسبيا من المعرفة حول الاكتئاب ولكن لديهم اتجاهات إيجابية نسبيا و يقومون ببعض الممارسات المرغوبة في معالجتهم للاكتئاب

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INTRODUCTION

Psychiatric disorder depressioncontributes significantly to the global burden of disease in developing countries. According to World Health Organization report, unipolar major depression will be the second leading cause of global burden of disease worldwide by 2020 (Who Report).[1] Another WHO study showed that in 15 primary care centers, 10.6% of all contacts was mainly due todepressive disorders.[2] Seventy six (76%) patients with affective disorder consult their general practitioner while 60% of people in the community seek professional assistance, even then depression is under-recognized and undertreated in primary care. There are various factors in patient, doctor and practice which contribute to the under-recognition and lack of optimal management of depression in general practice. Patient factors include co morbidity and stigma; doctor factors include inadequate knowledge and skills; practice factors include inadequate consultation time and insufficient access to specialized mental health resources. Somatic complaints are present in 80% of patients with a depressive or anxiety disorder which results in GPs' inability to recognize the origin of the patient's problem as depression or anxiety.[3]

In order to decrease depressive disorder a range of preventative and treatment strategies are urgently required. One of them may be providing the concept of 'mental health literacy that has emerged to describe "knowledge and beliefs about mental disorders which helps in recognition, management and prevention" of the depression which is not only common and disabling but it also responds to evidence-based treatments.[4]

WHO conducted a study in six centers showed that primaryhealth care staff lacked training in mental health and therefore had very limited knowledge of managing depression. Another study conducted in Campinas, Brazil, investigated the attitudes, knowledge, and self-reliance of primary care physicians to detect and treat depression found that 42% of the physician participants felt incompetent to differentiate between depression and unhappiness and 45% agreed that depression is a medical condition, 47% felt that depressive disorders is the outcome of tragedies in the person's life.[2]

Health professionals themselves have prejudiced attitudes and misperception about mental illness that it is incurable or self-inflicted can also be damaging for patients which results in impaired patient's referral to appropriate mental health care. Not only primary health care providers but even Psychiatrists themselves share the stigma of mental illness toward their patients. Also, the practice of psychiatry is often viewed as unscientific, imprecise and ineffective. Consequently, these primary care physicians tend to focus on physical symptoms and minimize diagnosis of mental disorder and are less likely to refer patients to mental-health services. Medical students judge psychiatrists to be emotionally unstable and 'woolly' thinkers but senior medical staffs often have more realistic attitudes towards mental illness than do their junior colleagues. This implies that the stigma of mental illness can be reduced by education and experience.[5]

A local study also revealed that the knowledge of family doctors about depression was quite low.One of the reasons for failure to detect psychiatric disorders include the lack of guidance for interviewing and diagnostic practices taught in medical schools. Primary care physicians fear loss of control, stigma and issues of time and money. The GPs misdiagnosis occurs because of not considering personal and family history and presence of stressful factors.[6]

This study was designed to assess the knowledge, beliefs and attitudes of medical professionals towards depressive disorder in Pakistan where mental health curriculum is limited to overcome the dearth of mental health problems and secondly KAP has not been estimated in Pakistan among Post graduate trainees or specialist. By conducting this survey magnitude of the problem can be assessed.

The objective of the study is to ascertain the current status of the knowledge, attitude and practice pertaining to depression among;
a) Access level of knowledge about depression among postgraduate trainees and specialist.
b) Access attitude and practicing trends among postgraduate trainees and specialist.

METHODS

This is survey research that was designed to explore the level of knowledge, attitude, and practice

patterns of post graduate trainees and specialists at CPSP centers from Karachi, Multan, Islamabad, and Peshawar cities of Pakistan. A survey was conducted from March to September 2013. All participants were recruited to study the research objective through purposive sampling technique. Data for the study was collected from selected participants after getting permission from president of CPSP.

Postgraduate trainees and non-psychiatric specialists who have attended CPSP workshops were included as inclusion criteria in the study. The exclusion criteria did not include doctors who were neither trainee nor psychiatric specialists were excluded from the study. After getting informed consent from participants, their demographic information including age, gender, professional status, and educational level were obtained. The data was collected by administering the self-constructed questionnaire that was designed to measure knowledge, attitude, and practices. It includes 08 items to assess participants' knowledge according to criteria for diagnosis of depression, 10 items which measure participants' attitude toward depression, and 07 items to assess practice patterns of participants.

Data Analysis:

Data was entered and analyzed by using the Statistical Package for Social Sciences (SPSS-17). Simple frequencies and percentages were computed to interpret research findings.

RESULTS

To assess doctors' knowledge about depressive disorder, we have constructed eight questions with four alternatives. They have to select the one, most appropriate answer out of four given alternatives.

As shown in table 1, the overall, ratio for correct answers is 47%, incorrect answers is 52%, and 1% respondents didn't reply to the asked question. It indicates that the level of knowledge of doctors about depressive disorder is not much satisfactory.

To measure doctors' attitude about depressive disorder, we have constructed 10 item Likert scale that ranged from 0=strongly disagree to 4=strongly agree. Results are shown in table 2; majority of doctors reported that despite assuming it difficult to work with the patient of depression they feel comfortable and gratified to invest their time in treating the

Table 1 Doctors' knowledge about depressive disorder

S.No.	Questions	Total participants	Correct Answer	Incorrect Answer	No Answer
1	Depressive disorder is diagnosed when it is continues for at least some days	263	93 (35%)	165 (63%)	5 (2%)
2	Core feature of depression	263	132 (50%)	130 (49%)	1 (0.38%)
3	Appetite of depressed patients	263	203 (77%)	59 (22%)	1 (0.38%)
4	Hopelessness is a feature of	263	147 (56%)	114 (43%)	2 (0.76%)
5	Pessimistic thoughts about present in depressive disorder	263	113 (43%)	144 (55%)	6 (2%)
6	Cognitive functions are impaired	263	131 (50%)	128 (49%)	4 (2%)
7	Suicidal thoughts are assessed by asking about suicide	263	111 (42%)	149 (57%)	3 (1%)
8	According to WHO Depression will be the Leading cause of disease burden worldwide by 2020	263	41 (16%)	216 (82%)	6 (2%)
Total		263	47%	52%	1%

patients of depression. Most of doctors are satisfied with the effectiveness of anti-depressive drugs and they assumed that psychotherapy has place in the treatment of depression. Additionally, they also believed that prescription of antidepressants and psychotherapy should be given by specialists.

To explored doctors' practice in the treatment of depression, the researchers have constructed seven statements. Results are shown in table 3, majority of doctors reportedly prescribed SSRIs although some of them also prefer to the combination therapy. Majority of doctors reported that they see less than five patients of depression in one week and they tended to refer them to the mental health specialist. Most of the doctors reported that most of the patients with depression report physical complain and the most associated physical complain with depression is headache.

DISCUSSION

This exploratory study was designed to explore medical professionals' level of knowledge, their attitudes, and general practice in the treatment of depressive disorder in Pakistani context. Our results indicate that doctors' knowledge level about depressive disorder

Table 2 Doctors' attitudes about depressive disorder, N=263

S.No.	Questions	Strongly Disagree	Disagree	Don't Know	Agree	Strongly Agree	No Answer
1	It is easy to differentiate between a patient who is sad and one who is depressed.	24 (9%)	28 (11%)	55 (21%)	44 (17%)	111 (42%)	1 (0.3%)
2	Working with depressed patients is difficult	29 (11%)	17 (6%)	43 (16%)	33 (13%)	140 (53%)	1 (0.3%)
3	Depression is a way that weak people confront life's problems	31 (12%)	53 (20%)	48 (18%)	44 (17%)	85 (32%)	1 (0.3%)
4	I am comfortable addressing the problems of patients with depression	23 (9%)	33 (13%)	58 (22%)	51 (19%)	94 (36%)	4 (2%)
5	Depression reflects a personality characteristic in the patient that is not easy to change	16 (6%)	81 (31%)	56 (21%)	26 (10%)	79 (30%)	5 (2%)
6	It is gratifying to invest time in treating depressed patients	47 (18%)	27 (10%)	30 (11%)	24 (9%)	123 (46%)	12 (5%)
7	Psychotherapy has no place for depressed patients	3 (1%)	165 (63%)	41 (16%)	15 (6%)	15 (6%)	10 (4%)
8	Antidepressants produce satisfactory results in treating depressed patients	33 (13%)	37 (14%)	35 (13%)	47 (18%)	104 (40%)	5 (2%)
9	Psychotherapy of depressed patients should be left to the specialist	24 (9%)	46 (17%)	80 (30%)	46 (17%)	62 (24%)	5 (2%)
10	Depressed patient who needs antidepressants should be treated by psychiatrist	47 (18%)	51 (19%)	58 (22%)	27 (10%)	70 (27%)	10 (4%)

is not satisfactory. It implies that they are not well aware about the symptomatological representation of depressive disorder. Consistent findings with our results are reported by other researchers in the scientific literature. For example Mahmood-Abadi, Kayhani, Rabi, and Mohammadi have conducted a cross sectional research in Iran on non-psychiatric physicians to assess their level of knowledge toward depression and found that non-psychiatric physicians reported low level of knowledge about depression.[7] Other researches also reported same evidences, that most of the physicians were not confident about their diagnosis of depressive disorder.[8, 9] Family physicians lack the necessary knowledge to diagnose and treat depression.[10] Most of the primary care physicians feel challenges to diagnose and treat bipolar disorders including depression.[11] Similar findings also reported by Jafri, Minhas, Tamiz-ud-Din, Slatch and Mujeeb in Pakistan. They have interviewed both educated community members with rural as well as urban

Table 3 Doctors' practice in treating depressive disorder, N=263

S.No.	Questions	Frequencies of Doctors' responses to the corresponding questions				No Answer
1	Which antidepressant do you prescribe more?	SSRI=146 (56%)	SNRI=22 (8%)	TCA=49 (19%)	Others = 15 (6%)	31 (12%)
2	Do you use combination of antidepressants?			Yes=78 (30%)	No=92 (35%)	93 (35%)
3	Which combination of antipsychotics and antidepressant you prescribe?	TCA-BENZO=33 (13%)	TCA-Antipsychotic= 102 (39%)	SSRI-BENZO= 38 (14%)	SSRI-Antipsychotic= 27 (10%)	63 (24%)
4	How many depressive patients you see in one week?	<5=141 (54%)	6-10= 61 (23%)	10-20= 12 (5%)	>20=5 (2%)	44 (17%)
5	How much you refer to mental health specialist?	<5=73 (28%)	6-10= 41 (16%)	10-20= 77 (29%)	>20=14 (5%)	58 (22%)
6	How many depressive patients report physical complain with depression?	<5=72 (27%)	6-10= 15 (6%)	10-20= 46 (18%)	>20=67 (25%)	63 (24%)
7	Types of pain associated with depression	Headache= 106 (40%)	Back pain= 37 (14%)	Gastric= 40 (15%)	Aches and Pain=61 (23%)	19 (7%)

Note: SSRI:selective serotonin reuptake inhibitors, SNRI: Serotonin and nor epinephrine reuptake inhibitors, TCA: tricyclic antidepressants, BENZO: Benzodiazepines

backgrounds and health care providers, where both community members and health care providers reported low level of knowledge about mental illnesses. Most of them considered drug abuse and addiction as common mental illness. When they asked about the symptoms of depression majority of the participants reported irritability as a major symptom of depression but according to DSM-V and ICD-10 this is an associated symptom of depression instead of major symptom.[12] Our findings and related empirical evidences indicate that non-psychiatric physicians treat depression without proper insight about the depressive disorder that is serious concern. If they treat without understanding and proper diagnosis the treatment may be ineffective or even harmful for the patients of depression.

The second objective of the study was to find out doctors attitudes about the treatment of depressive disorder. Somewhat mix findings were found about this objective. Majority of doctors believe that it is not difficult for them to differentiate between a patient who is sad and one who is depressed but they assumed that it is difficulttask for them to work with depressed patients. Mahmood-Abadi, Kayhani, Rabi, and Mohammadi also reported same findings where most of the non-psychiatric physicians perceived themselves as incapable to manage depression.[7] Despite having the sense of difficulty to work with the patients of depression,medical professionals in our studyfeel comfortable to address the problems of person with depression. Some research findings such as those reported by Mahmood-Abadi et al, most of the non-psychiatric physicians had little knowledge about the psychotherapy and the time duration it needs to take effect in the treatment of depression.[7] But medical professionals who have participated in our study were well aware about the concept of psychotherapy in the treatment of depression.They believe that psychotherapy has place in the treatment of depression and it should be given by its specialist. According to Casini, Sighinolfi, Tedesco, Bandieri, Bologna,Colombini, et al majority of primary care physicians agreed that the psychotherapy is effective in the treatment of depression and it should be left to a specialist and only 20% physicians reported that psychotherapy is ineffective in the treatment of depression, indicating

a general positive opinion about the psychological treatment of depression.[13] Some other researches claimed that according to general physicians, psychotherapy cannot replace antidepressants while some of them considered it as essential complement in the treatment of depression. Problem solving therapy as intervention for depression is a currently practicing approach and potentially useful to both general professionals and patients.[14, 15] Additionally, Mahmood-Abadi et al, fond that majority of non-psychiatric physicians were not much knowledgeable about the therapeutic indications and time needed for the antidepressants drugs to have effect. In contrast medical professionals in our study were satisfied about the effectiveness of antidepressants but they assumed that antidepressants should be prescribed by psychiatrist.

Finally, we have also explored medical professionals' general practice in the treatment of depressive disorder. Findings indicate that most of the doctors prescribe SSRIs to treat depression. These findings are in line with other evidences reported that primary care physicians agreed about the effectiveness of antidepressant drugs in the treatment of depression.[13] Some medical professionalism our study also reported that they use combination of drugs to treat depression. Antidepressants monotherapy is more prevalent among primary care physicians although it is relatively low among psychiatric regimens but combination treatment become more common among primary care physicians when they perceive that the severity of disease increases. The commonly used agents with antidepressants included another antidepressant, an anxiety agent, and atypical antipsychotic agents.[16] We have also observed somedesirable practices among medical professionals in our study that is they use to refer their patients to the mental health specialist. Stang, Frank, Yood, Wells, Burch, and Muma also found that most of the primary care physicians willingly refer their bipolar patients to the psychiatrist for the diagnosis and treatment in order to ensure the optimal care of their patients.[11] Additionally, respondents of the present study also believed that majority of patients with depression report physical complainsand the most associated physical complain with depression is headache. This claim of our respondent is consistent with other empirical evidences reported by Madhukar and Trivedi. According to them physical symptoms are common in depression. High number of patients with depression seeks treatment in the primary care setting report only physical symptoms.[17]

Conclusion

The present findings revealed that medical professionals in Pakistan tend to have relatively low level of knowledge about depressive disorder but still treating it that is serious concern. The positive aspect of medical professionals that we have found in this study is that they believe in the effectiveness of antidepressants and psychotherapy as effective interventions for depression and assumed to be provided these services by their specialist, so that most of the medical professionals reported that they use to refer their patients to mental health professionals.

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Nursing Students' Perceptions of Effective Clinical Teacher in Al'Majmaah District

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ABSTRACT

BACKGROUND & OBJECTIVES: Clinical education is a dynamic process and has an important role in training competent nurses. The clinical experience of nursing students is an important part of any nursing education program, and it is critical determinant for quality of clinical learning experiences. The clinical educators experience, knowledge and personality have an influence on the students. The researchers believed that a better understanding of the perceptions of effective clinical teacher among nursing students would enhance the clinical teaching. The aim of study is to explore the nursing student's perception on the characteristics of an effective clinical teacher in Majmaah University (KSA). **METHODS:** A descriptive study design using self-administered questionnaire of five domains was used which consisted of 44 items related to the most effective clinical characteristics. One hundred forty seven (n= 147) nursing students of Majmaah university participated in this study. **RESULTS:** All participants rated the Professional Nursing Competencies as the most important domain 4.34 (SD = 0.87), and the lowest important domain perceived by participants was teaching skills 4.01 (SD =1.04). "Demonstrates nursing skills and procedures proficiently" was the highest rated characteristics perceived by students' 4.5, (SD = 0.788), on the other hand the lowest characteristics was" Encourages Students to a critical way of thinking" to 4.33 (SD = 0.86). In addition, the results showed no significant difference in any of the five domains between male female students. These results synchronized with similar studies in other part of Arab and congruent with the students level of educations. **CONCLUSION:** Further studies need to validate the results to examine if there is any difference according to gender, academic levels or geographical variation in kingdom of Saudi Arabia.

Key words: Nursing student, Clinical teacher,

الملخص

يعتبر التعليم العملي والتدريب الاكلينيكي لطلاب تخصص التمريض في برامجهم المختلفة ومستوياتهم المتعدده حجر الزاوية في اكسابهم المهارات و الكفايات اللازمة للقيام بدرورهم كممرضين فاعلين , ومدرسي التمريض الاكلينيكي هم الرقم الصعب في هذه العملية من خلال الكفايات والصفات التي يمتلكونها, والسلوكيات و الاستراتيجيات التي يتبعونها في اكساب الطلاب لهذه المهارات. **هدفت الدراسة** الى تحديد اهم الصفات التي يجب توافرها في المدرس الاكلينيكي الفعّال من وجهة نظر طلاب التمريض حسب انطباعاتهم عن التدريب العملي الاكلينيكي. ويعتقد الباحث أن فهم وادراك طلاب التمريض في محافظة المجمعة لصفات مدرس التمريض الاكلينيكي الفعّال, يؤدي لتطويرها والوصول إلى تعليم وتدريب فاعل ومؤثر يحقق الاهداف المرجوة من التدريب الاكلينيكي, والتركيز على كيفية توافرها وديمومتها بالشكل الفعال لدى المدرسين والعمل على بناء برامج تدريبية وتطويرية لزيادة كفاءتهم. **منهجية الدراسة :** قامت هذه الدراسة على منهجية الدراسات المسحية والوصفية من خلال بناء استبانة ذاتية يجيب عليها الطلاب بانفسهم وتحتوي على قائمة بأهم الصفات الواجب توافرها في المدرس الاكلينيكي, اشتملت على على اربعة واربعين (44) فقرةً جاءت في خمس مجالات رئيسة, و بمشاركة مائة وسبعة وأربعون (147) طالباً وطالبةً من اقسام التمريض في جامعة المجمعة. **النتائج:** اشارت النتائج ان مجال «الكفايات المهنية التمريضية» حاز على درجة الاهمية الاعلى من وجهة نظر أفراد العينة بمتوسط حسابي مقداره (4.34) درجة وانحراف معياري (0.87) ، وحاز مجال» مهارات التدريس» على درجة الاهمية الاقل بمتوسط حسابي مقداره (4.01) درجة وانحراف معياري (1.04), وحازت فقرة « يطبق المهارات والإجراءات التمريضية بإتقان « على درجة الاهمية الاعلى بمتوسط حسابي مقداره (4.5) درجة وانحراف معياري (0.788)، فيما حصلت فقرة « يشجع الطلاب على استخدام التفكير الناقد» على درجة الاهمية الاقل بمتوسط حسابي مقداره (4.33) درجة وانحراف معياري (0.86). وبالإضافة إلى ذلك، أظهرت النتائج عدم وجود فروق ذات دلالة إحصائية عند مستوى (α = .05) في أي من المجالات الخمسة بين الطلاب والطالبات. وتتفق هذه النتائج مع بعض الدراسات المماثلة في بعض الدول العربية ومتطابقة مع مستوى الطلاب التعليمي.**التوصيات:** استناداً إلى نتائج الدراسة يوصي الباحث باجاء المزيد من الدراسات للتحقق من صحة نتائج هذه الدراسة وقياس ما إذا كان هناك وجود فروق ذات دلالة إحصائية وفقا لنوع الجنس، والمستويات الأكاديمية أو التباين الجغرافي في المملكة العربية السعودية.

INTRODUCTION

Nursing is a very challenging profession that require integration educational curriculum including the theoretical learning and clinical learning. Clinical training provide student with knowledge, skills and communication abilities. Beside the curriculum content that proposed 50% should take place in the clinical environment or setting.[1] Educators play a vital role in clinical setting too. Nursing clinical

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educator are responsible for insuring that students have to learn how to apply theory, gain hands - on experience, practice technique, and develop into mature people.[2] In addition to offer positive and conductive learning environment,[3,4] the close working relationship between student and educator made student nominate clinical training as the most influential context for acquiring knowledge and nursing skills.[5]

Clinical teacher should be professional, qualified, expert and able to insure patient safety as well as quality care,[6] despite the need for effective clinical education, the criteria for determining effective clinical teaching remain poorly defined,[7,8] and the role of the nurse teacher lacks clarity,[9] Teacher effectiveness is more difficult to evaluate in diverse, often fast paced, highly complex clinical setting, than more controlled environments such as seminars, laboratory and classrooms,[7,8] here is urgent and compelling need to gain better understanding of what constitutes and characteristics of effective clinical teaching the studies in this topic indicate that the professional competence, interpersonal relationship skills, personality characteristics, and teaching ability were the main qualification of successful clinical teacher.[10-11]

Both the training context and the qualification of the clinical educator can effectively contribute in enhancement students clinical performance. The student weakness ,complains and male performance of Majmaah University trigger the researcher to find out what characteristics is most important by nursing students in relation to effective clinical teachers. The purpose of this study is to identify the characteristics of effective nursing clinical teachers from student perspective in Majmaah University. The aim of the present study was to explore the effective clinical teacher characteristics by answering the following research question

1. What are the characteristics of effective clinical teachers at Majmaah University?
2. What is the degree of importance of characteristics of effective clinical teachers at Majmaah University
3. Is there any significant difference in what female and male nursing students perceive as important characteristics of effective clinical teachers?

METHODS

Study Design:

A descriptive design was used for this study. Nursing students of Applied Medical Sciences at Majmaah University (MU), Majmaah, KSA, were invited to participate in this study. During the first trimester of 1432-1433 data was collected in the nursing department (female and male) section. Since 2010, MU is the only university that offers a baccalaureate in nursing (B.Sc. N) in the north region of Riyadh

Sample population:

One hundred and eighty one (181) nursing student who enrolled in the baccalaureate degree program in Nursing Department of Applied Medical Sciences (Females and Males Sections were eligible for the study. To be eligible, student had to have clinical training at least one semester prior to the study, and agreed to participate in the study. The participants were recruited by faculty section's level coordinators, who were helped by the facility members in each day or/and location. After informed consent, student were interviewed in their clinical and lecture room in both college section by coordinators and faculty member to discuss the purposes of the study, to read the covering letter and to answer any questions about the study. After the interview, the participants were asked to complete a questionnaire about the nursing students' perceptions of effective clinical teacher.

Validity and reliability:

The questionnaire was developed specifically for this study by the authors based on review of the literature. After four experts evaluation, a minor change was made (rebuild and omit some items). Content validity for the questionnaire was determined by the expertise. For reliability, Testing the stability of returns (test-retest) estimates at 2 weeks, the questionnaire had an internal consistency/ Cronbach's alpha of (0.89) and acceptable internal consistency of the five domains. Psychometric results indicated that this questionnaire is a valid and reliable. Cronbach's alpha reported for this tool ranged from α=0.70 to 0.94 and the Pearson correlation coefficient ranged from 0.80 to 0.90.

Ethical Considerations: The study was approved by the Institutional Ethical Research Committees in Basic & Health Sciences Research Centre, MU. Potential participants were informed the purpose

of the study with detailed explanation and further enquired if they agreed to participate in the study. Furthermore, participants were told that the participation was optional and their responses would remain anonymous. The researchers include informed consent form within the cover letter to encourage students to participate in this research.

Data Analysis: Statistical Package for the Social Sciences (SPSS) version 17 was used for statistical analysis. To detect the degree of importance and the Domains of characteristics of effective clinical teachers, the researchers adopted a five-scale grading, which were given weighted scores of the importance of characteristics of effective clinical teachers. These rankings were represented as Means. The responses to the survey item statements were analyzed using frequency and percent, measures of central tendency including the mean, mode, and median. Standard deviations were analyzed to measure the dispersion of the results. Both the measures of central tendency and measures of dispersion were presented in narrative form or in tables.

RESULTS

One-hundred eighty one students who met the inclusion criteria were approached for participation in the study. Of these students, 147 returned completed questionnaires and 34 did not respond or returned incomplete questionnaires resulting in 81% response rate. Seventy-nine (81.4%) were female and 68 (80.9%) were male. The age range was between 18 and 23. All the participants were in the Level II to Level VIII.

Characteristics of clinical teachers at Majmaah University

Based on the retrieved data, (as shown in Figure 1) majority of the nursing students perceived professional nursing competencies as an effective characteristic domain of clinical teachers. However, the participants determined teaching skills, personality characteristics, student's evaluation and interpersonal characteristics as other characteristic domains respectively.

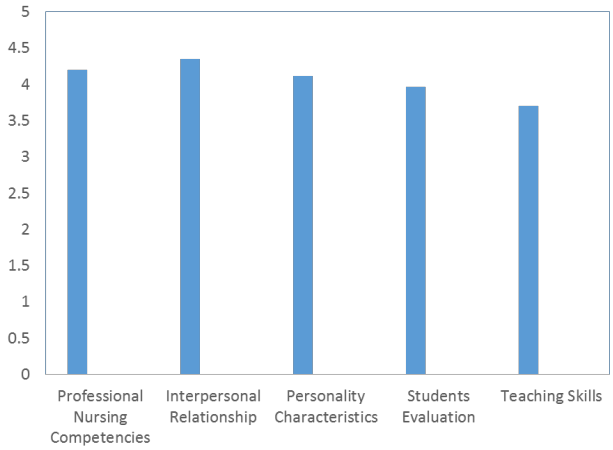

Figure 1: Means, Standard deviation, a for each of the five Domains, (n = 147)

Degree of importance of characteristics of effective clinical teacher at Majmaah University

Based on the retrieved data, it was shown that students perceived professional nursing competencies domain as the most effective domain of clinical teacher with mean range of 4.20. (SD = 0.94) Whilst, interpersonal relationship characteristics mean range of 4.35 (SD = .98); personality characteristics domain mean range of 4.12 (SD = 1.3); students evaluation domain mean range 3.97 (SD = 1); and teaching skills mean range of 3.7 (SD = 1.2).

Significance of difference between the perceptions of female and male nursing students on the characteristics of effective clinical teachers

Table (1) shows that the mean (±SD) scores of the

Table 1: Result of Mean Score for Five Domains of the Characteristics of the Clinical Teacher for Female and Male and t- test Significance.

No.	Domains	Female		Male		T	*P
		Mean	SD	Mean	SD		
1	Teaching Skills	3.99	1.00	4.10	0.72		
2	Professional Nursing Competencies	4.30	0.82	4.50	0.66	0.699	0.090
3	Personality Characteristics	4.23	0.97	4.37	0.83	0.593	0.550
4	Interpersonal Relationships	4.30	1.00	4.37	0.85	0.417	0.678
5	Students Evaluation	4.16	1.00	4.21	0.70	0.287	0.775

five domains respectively. Professional nursing competence scores by female student are significantly different from the male student. This section tested the null hypothesis that there is no significant difference between the perceptions of female and male nursing students on the characteristics of effective clinical teachers. Analysis of the data revealed that the male group perceived professional nursing competencies as the characteristic domain of effective clinical teacher (mean = 4.5) followed by personality characteristics and interpersonal relationships (mean = 4.37); students evaluation (mean = 4.21) and teachings skills (mean = 4.1) respectively. However, the female group rated professional nursing competencies and interpersonal relationships (mean = 4.3); personality characteristics (mean= 4.23); students evaluation (mean = 4.16) and teaching skills (mean = 4.37).

Discussion

The reviewed literature revealed that the main characteristics to perform effective clinical teaching are: the nursing competencies, interpersonal relationship skills, personality characteristics, teaching ability and evaluation.[10-12]

In the domains rating the students showed that the most important domain is “Professional Nursing Competencies” and the least rating one is the “Students Evaluation and Teaching Skills” and this is consistent with other studies conducted in Arab countries and was different to that of other studies conducted in USA , Canada , UK or Australia.[13-16]

This finding's reflected the culture belief about teacher who is consider the center of the teaching process and the main information giver, according to[17] students have a high regard for their teachers who are knowledgeable and competent. UK and Australia studies found that clinical competence and clinical credibility of nurse teachers have been the focus of much debate[14,18]. Evaluation and teaching skills is rating in lowest important and this is not synchronize with western studies investigated the students perception this can be explained with the context of traditional views for teacher personality.

In the “Professional Nursing Competencies” domain; students rated the item of '' Demonstrates nursing skills and procedures proficiently indicate the importance of nursing skills on the minds of nursing students rated categories regarding supervision and distribution the lowest importance in this domain which reflected more desire for some freedom in those items.

The item of “Shows cooperative attitude” in Personality Characteristics Domain was rated the most important one by the participants and the lowest was "Shows patience attitude”. This shows the need of cooperation between clinical teacher and the students.

In Students Evaluation Domain: Most of the participants rated the item related to “Follows Students progress in clinical sitting” which shows the importance for the students in clinical sitting to follow their progress marks and achievement, also they rated the item “Accepts individual differences in students” the poorest item, which reflected feel with no major difference between themselves.

In the domain of “teaching skills” the students rating the item of “explains clearly” is the most important one in this domain and this is reflected that students are teacher centered and they considered him as the main information source so this item takes the highest rating. Another study[19,20] stated that students always expert their clinical preceptor to be able to offer them clear explanations and reasonable practical knowledge. The lowest item rated by the students in this domain was the item which “encourages students to a critical way of thinking.” This reflected that the students didn’t pay attention for this item which reflected the poor using of this method of teaching from the clinical teachers and their focus on the traditional old way of teaching.

Conclusion

The findings of this study support the importance of maintaining clinical competence of the nurse teachers if they want to be considered as good role models for their students as well as to maintain their credibility as good teachers. The results indicated that nursing competencies are perceived by the participant students as the most important characteristics of effective clinical teacher followed by the interpersonal relationships in the 2nd place, personality characteristics in the 3rd place and student evaluation in the 4th place, and the last in this category was teaching skills. This rank order agrees with some

previous research and disagrees with others, some of the participants still didn't enter enough time in clinical teaching because they still are in early levels of nursing and others sometimes are instructed by hospital staff nurses who were not prepared well. Another reason is our classification of different characteristics in five domains which is unique from many other published researches. A further study is required to validate the results and to examine if there is any differences according academic levels or different districts in KSA.

LIMITATIONS

- Data collection was limited to those students who attended baccalaureate degree program.
- Part of data described perceptions of beginning level student.
- Survey design reflected self-reported data based on recall.

ACKNOWLEDGEMENT

The author is grateful to all Nursing students, for spending valuable time from their study, for my colleagues in female section to help with data collection, and the administration of the library for providing access to their database. Finally would like to thank the Basic & Health Sciences Research Centre under Deanship of Scientific Research, Majmaah University for their support and contribution to this study.

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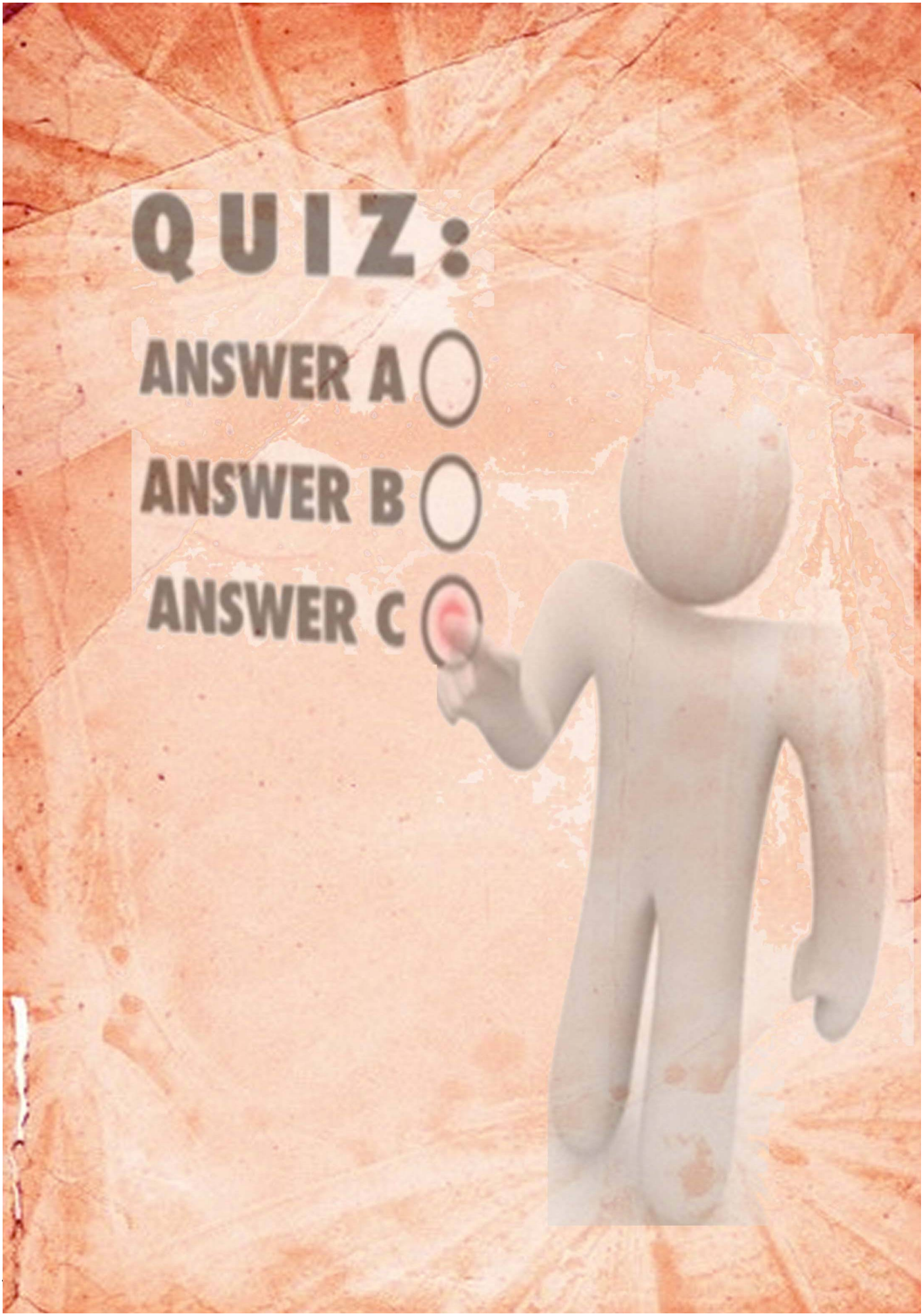
QUIZ:
ANSWER A
ANSWER B
ANSWER C

MEDICAL QUIZ

DR. AHMED MERAJ

A 32 year old male came to the medicine OPD with complaints of gradual onset of pain and stiffness in the lower back and upper buttock area since the past 8 months. This has progressively worsened with loss of range of motion since the past few months.

He also stated that symptoms of pain and stiffness were often worse in the morning or after prolonged periods of inactivity. This would gradually reduce during the day due to moving about or applying heat to the affected part. A couple of weeks earlier he had developed a respiratory infection for which he took some medications. After that he has had on-off episodes of cough and shortness of breath which has prevented him from doing his daily routine of exercises. Recently he has developed an irritation in his right eye which worsens on exposure to bright light.

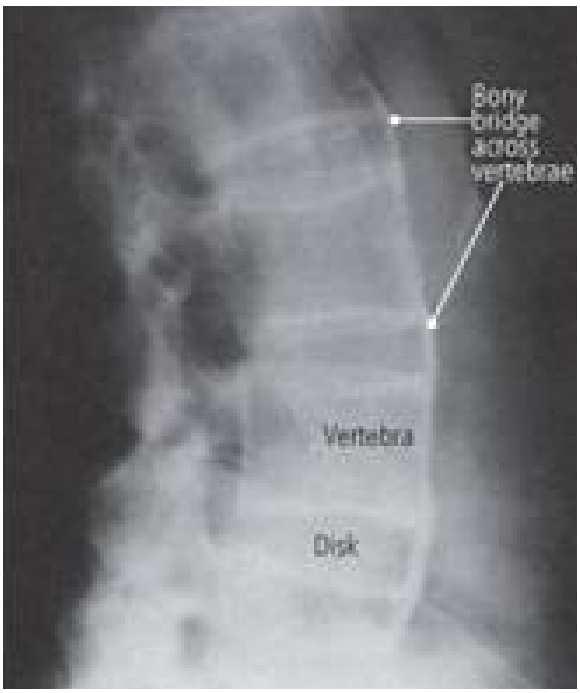

Figure – 1 (lateral X-ray of spine)

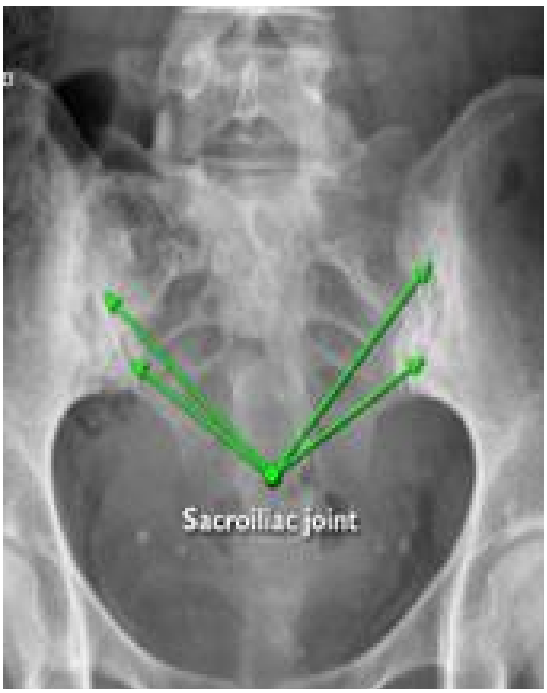

Figure – 2 (AP X-ray of Sacroiliiac)

EXAMINATION

The patient has a stooped posture. There is decreased range of movement of the spine and tenderness of the sacroiliac joints of the upper buttocks is present. There is limited expansion of the chest wall with full breathing and ophthalmoscopy revealed acute anterior uveitis.

INVESTIGATION

- Blood investigation shows normochromic, normocytic anemia with a raised ESR and CRP levels. Alkaline Phosphatase level is elevated.
- X-ray shows sacroiliitis and “squared” vertebral bodies with bony bridges across vertebrae.

Quiz

1. Which of the following is a correct diagnosis of the above case?

a. Juvenile Idiopathic Arthritis
b. Ankylosing spondilitis
c. Enteropathic Arthropathy
d. Sacroiliac joint dysfunction

2. Which of the following drug can be given in this disorder which is poorly controlled with NSAIDs?

a. Infliximab
b. Methotrexate
c. Sulfasalazine
d. Adalimumab

3. Which of the following spinal examination will be positive in a patient of the above disorder?

a. Tenderness of a specific vertebrae along the spine
b. Scoliosis of the spine is positive
c. Shober's test reveals lumbar flexion restriction
d. Cervical lordosis is present in the patient

4. Which of the following extra-articular feature is present in the above disorder?

a. Apical pulmonary fibrosis
b. Pulmonary artery regurgitation
c. Peripheral neuropathy
d. Aortic stenosis

The answers are 1 (B) 2 (D) 3 (C) 4 (A)


Medical News
NEWS


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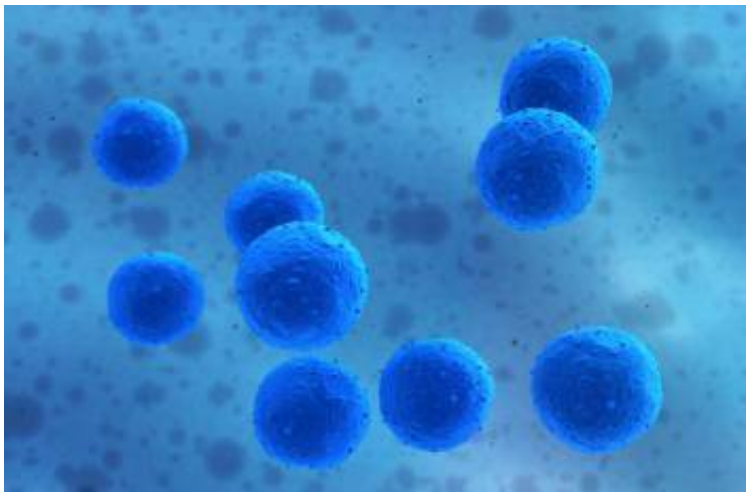
STEM CELL BREAKTHROUGH: PATIENT-SPECIFIC THERAPIES FOR TYPE 1 DIABETES

A team of scientists from the New York Stem Cell Foundation Research Institute and Columbia University Medical Center, also in New York, claim to have created the first disease-specific embryonic stem cell line with two sets of chromosomes.

- The research began in 2006 as part of an effort to make patient-specific embryonic stem cell lines from people who have type 1 diabetes.
- The process behind this innovation is called somatic cell nuclear transfer (SCNT). It involves taking unfertilized donor oocytes - the immature egg cells used in reproduction - and adding to them the nuclei of adult skin cells taken from the patient.
- Stem cell experiments for this project initially took place at Harvard University in Cambridge, MA, with skin biopsies from the patients being performed at Columbia University Medical Center.
- However, isolating cell nuclei from skin biopsies was not possible in the federally funded Columbia labs. As a solution, the New York Stem Cell Foundation Research Institute (NYSCF) opened its own privately-funded laboratory to complete the research - now the largest independent stem cell laboratory in the US.
- By 2008, all of the research had been moved to the NYSCF lab, as Massachusetts restrictions prevented Harvard from obtaining oocytes.
- In an associated news release, the NYSCF say that "the reprogramming of skin cells from a type 1 diabetes patient by SCNT has long been sought," but that progress within this field has been stymied by difficulties in obtaining oocytes for research, as well as an incomplete understanding of the biology of human oocytes.



SCNT progress has been stymied by difficulties in obtaining oocytes for research, as well as an incomplete understanding of their biology.

Lab-created insulin-producing beta cells could offer a cure for type 1 diabetes

People with type 1 diabetes are deficient in insulin and have high blood sugar levels because they lack insulin-producing beta cells. Therefore, if beta cells can be successfully produced from stem cells, they could be transplanted into diabetic patients as a treatment and potential cure. As the stem cells are made from the patient's own skin cells, they would all match the patient's DNA.

In 2011, the scientists reported that they had created the first embryonic stem cell line from human skin using nuclear transfer. However, the stem cells produced had three sets of chromosomes and could not be used as a treatment. But the scientists have now been able to create a patient-specific embryonic stem cell line that has two sets of chromosomes, which is the normal number in human cells.

Dr. Dieter Egli, the NYSCF scientist who led the research, says:
"From the start, the goal of this work has been to make patient-specific stem cells from an adult human subject with type 1 diabetes that can give rise to the cells lost in the disease. By reprogramming cells to a pluripotent state and making beta cells, we are now one step closer to being able to treat diabetic patients with their own insulin-producing cells."

However, this is not the end of this research; the success in producing the patient-specific cells only marks the completion of the first phase of the project. The next step is to develop strategies that prevent the immune systems of type 1 diabetes patients from attacking their own beta cells.

Co-author, Dr. Rudolph Leibel, says:
"This accomplishment is the product of an ongoing inter-institutional collaboration across scientific and clinical disciplines, supported by thoughtful philanthropy. The resulting technical and scientific insights bring closer the promise of cell replacement for a wide range of human disease."

In 2012, Medical News Today reported on research published in PLOS One that discovered stem cells in the pancreas can be turned into insulin-producing cells. The researchers behind that study claimed that the potential to regenerate insulin-producing cells is present in all of us, and suggested that further research along these lines may provide a cure for type 1 diabetes.

Are Seniors With Diabetes Overtreated?
Very tight blood sugar control can pose problems without benefits, study says

WebMD News from HealthDay
By Dennis Thompson
HealthDay Reporter

MONDAY, Jan. 12, 2015 (HealthDay News) -- Many older people with diabetes may be exposed to potential harm because doctors are trying to keep overly tight control of their blood sugar levels, a new study argues.

Researchers found that nearly two-thirds of older diabetics who are in poor health have been placed on a diabetes management regimen that strictly controls their blood sugar, aiming at a targeted hemoglobin A1C level of less than 7 percent. But these patients are achieving that goal through the use of medications that place them at greater risk of hypoglycemia, a reaction to overly low blood sugar that can cause abnormal heart rhythms, and dizziness or loss of consciousness, the researchers said.

Further, tight diabetes control did not appear to benefit the patients, the researchers report Jan. 12 in JAMA Internal Medicine. The percentage of seniors with diabetes in poor health did not change in more than a decade, even though many had undergone years of aggressive blood sugar treatment. "There is increasing evidence that tight blood sugar control can cause harm in older people, and older people are more susceptible to hypoglycemia," said lead author Dr. Kasia Lipska, an assistant professor of endocrinology at Yale University School of Medicine. "More than half of these patients were being treated with medications that are unlikely to benefit them and can cause problems."

Diabetes is common among people 65 and older. But doctors have struggled to come up with the best way to manage diabetes in seniors alongside the other health problems they typically have, researchers said in background information with the study. For younger and healthier adults, the American Diabetes Association has recommended therapy that aims at a hemoglobin A1C level of lower than 7 percent, while the American Association of Clinical Endocrinologists recommends a target of lower than 6.5 percent, the authors noted. The A1C test provides a picture of your average blood sugar levels for the past two to three months.

By tightly controlling blood sugar levels, doctors hope to stave off the complications of diabetes, including organ damage, blindness, and amputations due to nerve damage in the limbs.

SWINE FLU OUTBREAK IN INDIA RAISES CONCERN

MIT study finds evidence that a new strain of H1N1 may carry dangerous mutations

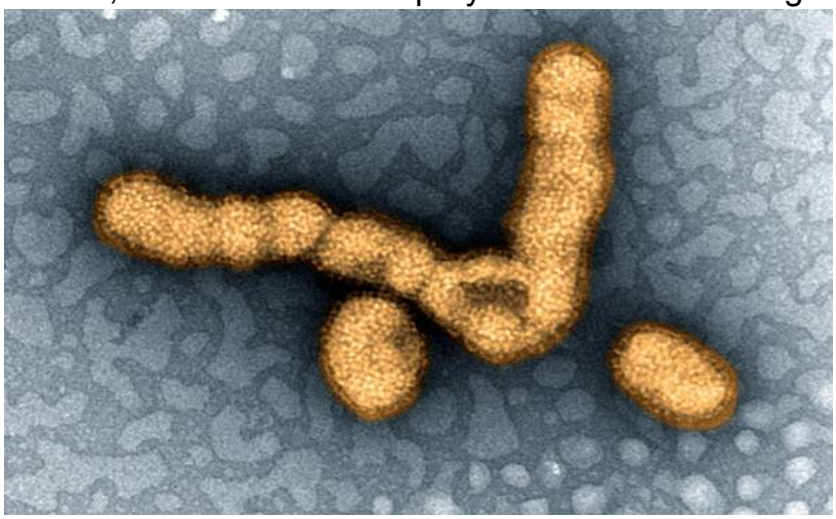
Anne Trafton
MIT News Office March 11, 2015

Since December, an outbreak of swine flu in India has killed more than 1,200 people, and a new MIT study suggests that the strain has acquired mutations that make it more dangerous than previously circulating strains of H1N1 influenza.

The findings, which appear in the March 11 issue of Cell Host & Microbe, contradict previous reports from Indian health officials that the strain has not changed from the version of H1N1 that emerged in 2009 and has been circulating around the world ever since.

With very little scientific data available about the new strain, the MIT researchers stress the need for better surveillance to track the outbreak and to help scientists to determine how to respond to this influenza variant.

"We're really caught between a rock and a hard place, with little information and a lot of misinformation," says Ram Sasisekharan, the Alfred H. Caspary Professor of Biological Engineering at MIT and the paper's senior author. "When you do real-time surveillance, get organized, and deposit these sequences, then you can come up with a better strategy to respond to the virus."



In the past two years, genetic sequence information of the flu-virus protein hemagglutinin from only two influenza strains from India has been deposited into publicly available influenza databases, making it difficult to determine exactly which strain is causing the new outbreak, and how it differs from previous strains. However, those two strains yielded enough information to warrant concern, says Sasisekharan, who is also a member of MIT's Koch Institute for Integrative Cancer Research.

He and Kannan Tharakaraman, a research scientist in MIT's Department of Biological Engineering, compared the genetic sequences of those two strains to the strain of H1N1 that emerged in 2009 and killed more than 18,000 people worldwide between 2009 and 2012.

The researchers found that the recent Indian strains carry new mutations in the hemagglutinin protein that are known to make the virus more virulent. Hemagglutinin binds to glycan receptors found on the surface of respiratory cells, and the strength of that binding determines how effectively the virus can infect those cells.

One of the new mutations is in an amino acid position called D225, which has been linked with increased disease severity. Another mutation, in the T200A position, allows hemagglutinin to bind more strongly to glycan receptors, making the virus more infectious.

"Aggressive surveillance"

Sasisekharan points out that more surveillance is needed to determine whether these mutations are present in the strain that is causing the current outbreak, which is most prevalent in the Indian states of Gujarat and Rajasthan and has infected more than 20,000 people so far.

"The point we're trying to make is that there is a real need for aggressive surveillance to ensure that the anxiety and hysteria are brought down and people are able to focus on what they really need to worry about," Sasisekharan says. "We need to understand the pathology and the severity, rather than simply relying on anecdotal information."

Learning more about the new strains could help public health officials to determine which drugs might be effective and to design new vaccines for the next flu season, which will likely include strains that are now circulating.

"The goal is to get a clearer picture of the strains that are circulating and therefore anticipate the right kind of a vaccine strategy for 2016," Sasisekharan says.

David Topham, a professor of microbiology and immunology at the University of Rochester, agrees there is a strong need for more influenza surveillance.

"Western scientists are just not paying enough attention to what's going on in such a large country as India. If anybody is collecting viruses and sequencing them, they're not being entered into one of the more common databases where people can look at them," says Topham, who was not involved in the research. "We're missing a big piece of the puzzle."

The research was funded by the National Institutes of Health, the National Research Foundation through the Singapore-MIT Alliance for Research and Technology, and the Skolkovo Foundation.

GUIDELINES FOR MANUSCRIPT PREPARATION

A. TYPES OF MANUSCRIPTS

I. ORIGINAL MANUSCRIPTS

Manuscripts submitted in this category are expected to be concise, well organized, and clearly written.
The maximum length is 5000 words, including the abstract, references, tables, and figure legends. The maximum length is 5000 words, including the abstract, references, tables, and figure legends.

- The structured abstract must not exceed 250 words.
- The title must not exceed 130 characters.
- A maximum of 4 tables and 4 figures is allowed.
- References should not exceed a maximum of 100.
- The abstract must be organized as follows:
- Background & Aims
- Methods
- Results
- Conclusions
- Do not use abbreviations, footnotes or references in the abstract.
- An electronic word count of the abstract must be included.
- Three to ten key words at the end of the abstract must be provided.

The manuscript must be arranged as follows:

- Title page
- Abstract
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Acknowledgements
- References
- Tables
- Figure legends
- Figures

Acceptance of original manuscripts will be based upon originality and importance of the investigation. These manuscripts are reviewed by the Editors and, in the majority of cases, by two experts in the field. Manuscripts requiring extensive revision will be at a disadvantage for publication and will be rejected. Authors shall be responsible for the quality of language and style and are strongly advised against submitting a manuscript which is not written in grammatically correct English. The Editors reserve the right to reject poorly written manuscripts even if their scientific content is qualitatively suitable for publication. Manuscripts are submitted with the understanding that they are original contributions and do not contain data that have been published elsewhere or are under consideration by another journal.

II. REVIEW ARTICLES

Review articles on selected clinical and basic topics of interest for the readers of the Majmaah Journal of Health Science will be solicited by the Editors. Review articles are expected to be clear, concise and updated.

- The maximum length is 5000 words, excluding the summary, references, tables, and figures.
- References should not exceed a maximum of 150.
- The inclusion of a maximum of 4 high-quality tables and 4 colored figures to summarize critical points is highly desirable.
- Review articles must be accompanied by a title page and a summary.

- Reviews should include at least one Key Point Box, with a maximum of 5 bullet points, that briefly summarizes the content of the review.

Review articles are reviewed by the Editors and may be sent to outside expert reviewers before a final decision for publication is made. Revisions may be required.

III. EDITORIALS

This section consists of invited brief editorial comments on articles published in the Majmaah Journal of Health Science

The length of an editorial should not exceed 1500 words, excluding references.

- A maximum of 1 table or 1 figure is allowed.
- References should not exceed a maximum of 20.
- A title page must be provided.

IV. CASE REPORTS

Case reports would be only accepted if they represent an outstanding contribution to the Etiology, pathogenesis or treatment of a specific condition.

- The maximum length is 3000 words, including the summary and references.
- A maximum of 2 tables and 2 figures is allowed.
- References should not exceed a maximum of 15.
- A title page must be provided.

V. LETTERS TO THE EDITOR

Letters to the Editor will be considered for publication if they are related to articles published in recent issues of Majmaah Journal of Health Science. Occasionally, Letters to the Editor that refer to articles not published in Majmaah Journal of Health Science will be considered.

The length of a Letter to the Editor should not exceed 800 words.

- A maximum of 1 table or 1 figure is allowed.
- References should not exceed a maximum of 10.
- No more than 4 Authors may appear in the author list.

VI. COMMENTARIES

International commentaries will be solicited by the Editors only.

- Commentary articles should not exceed a maximum of 800 words, excluding tables or figures.
- A maximum of 1 table or 1 figure is allowed.
- References should not exceed a maximum of 10.
- A title page must be provided.

B. MANUSCRIPT SUBMISSION

ORGANIZATION OF THE MANUSCRIPT

- The submitted manuscript must be typed double-spaced throughout and numbered (including references, tables and figure legends). Preferably using a "standard" font (we prefer Times/Arial 12).
- For mathematical symbols, Greek letters, and other special characters, use normal text. The references must be in accordance with the Vancouver reference style (see References).
- Approved nomenclature for gene and protein names and symbols should be used, including appropriate use of italics (all gene symbols and loci, should be in italics) and capitalization as it applies for each organism's standard nomenclature format, in text, tables, and figures.
- Full gene names are generally not in italics and Greek symbols are not used. Proteins should not be italicized.
- Improperly prepared manuscripts will not be entered into the peer review process and will be sent back to the author for correction.

TITLE PAGE MUST CONTAIN:

- A title of no more than 130 characters.

- Running title (not to exceed 60 characters)
- Names of the Authors as it should be published (first name, middle initial, last name)
- Affiliations of all authors and their institutions, departments, or organizations (use the following symbols in this order to designate authors' affiliations: *, †, ‡, §, ¶, ||, #, **, ††, ‡‡, §§, ¶¶, || ||, ##).
- Name, address, telephone and fax numbers, and electronic mail address of the corresponding Author.
- Electronic word count.
- Number of figures and tables.
- List of abbreviations in the order of appearance.
- Conflict of interest.
- Financial support.

Animal trials: Manuscripts reporting experiments using animals must include a statement giving assurance that all animals received human care and that study protocols comply with the institution's guidelines. Statistical methods used should be outlined.

Human trials: Manuscripts reporting data from research conducted on humans must include a statement of assurance in the methods section of the manuscript reading that:

1. Informed consent was obtained from each patient included in the study and
2. The study protocol conforms to the ethical guidelines of the 1975 declaration of helsinki as reflected in a priori approval by the institution's human research committee.

Randomized controlled trials: Any paper that is a randomized control trial should adhere to the guidelines that can be found at the following web-site: www.consort-statement.org. The checklist should be printed out and faxed to the Editorial office at the time of submission. The trial registration number must be included on the title page of the manuscript reporting a registered clinical trial. Failure to do so will prevent entry to the peer review process.

Drugs and chemicals: Drugs and chemicals should be used by generic name. If trademarks are mentioned, the manufacturer's name and city should be given. All funding sources supporting the work, either public or private, especially those from pharmaceutical companies, must be provided.

Genetic Sequence data: In papers reporting a novel DNA or amino sequence, verification that the data have been or will be submitted either to Gen-Bank or EMBL is required. Please provide this verification and the accession number in the covering letter.

REFERENCES

References must be in accordance with the Journal of Hepatology reference style. References are ordered as they appear in the text and citation numbers for references are placed between "brackets" ("[ ]") in the text as well as in the reference list.

Authors should be listed surname first, followed by the initials of given names (e.g. Bolognesi M). If there are more than six authors, the names of the first six authors followed by et al. should appear.
Titles of all cited articles are required. Titles of articles cited in reference list should be in upright, not italic text; the first word of the title is capitalized, the title written exactly as it appears in the work cited, ending with a full stop. Journal titles are abbreviated according to common usage, followed by Journal years, semicolon (;) before volume and colon (:) before full page range (see examples below).

All articles in the list of references should be cited in the text and, conversely, all references cited in the text must be included in the list.

Personal communications and unpublished data should be cited directly in the text by the first Author, without being numbered. Please make sure you have the latest, updated version of your reference management software to make sure you have the correct reference format for Majmaah Journal of Health Science.

An example of how references should look within the text:

"HVPG was measured by hepatic vein catheterization using a balloon catheter according to a procedure described elsewhere [14, 15] and used as an index of portal hypertension [16]."

An example of how the reference list should look:

[14] Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology 1992;102:973-979.
[15] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280-282.

FIGURES

A maximum of 4 figures is allowed
(This can be modified if needed by Editorial board).

- Figures will be often, but not always, re-designed by graphic designers. By signing and transferring the Copyright Agreement to MJHS, the author gives permission to the graphic designers to alter the visual aspect of any figures, tables, or graphs. The scientific content of figures will not be altered. Please provide this information with your covering letter.
- All graphics submitted to Majmaah Journal of Health Science should be sent at their actual size, which is 100% of their print dimension and in portrait orientation.
- Two standard widths are used and figures should fit in one (8.5 x 23.5 cm) or two (17.5 x 23.5 cm) columns
- Figures should be supplied in the following preferred file formats: PDF (*.pdf), Power Point (*.ppt), Adobe Illustrator (*.ai, *.eps), Photoshop (*.psd) files in grayscales or in RGB color mode. It is highly recommended that figures not be sent in JPG (*.jpg) format.
- Photographs (scans, immunofluorescences, EM, and histology images) should be submitted as: 1. TIFF (*.tif) with a resolution of at least 300 pixels per inch, or
- Illustrator compatible EPS files with RGB color management (*.eps),
- Photoshop (*.psd) or PDF (*.pdf) files (grayscales or RGB) at the appropriate resolution, which is:

1. 300 dpi for color figures
2. 600 dpi for black and white figures
3. 1200 dpi for line-art figures

- For all photomicrographs, where possible, a scale should appear on the photograph. Photographs of identifiable patients should be accompanied by written permission to publish from patient(s).
- • Furthermore, panel lettering should be in Arial bold 14 pt, capitalized and no full stop (A, B) while lettering in figures (axes, conditions), should be in Arial 8 pt, lower case type with the first letter capitalized and no full stop. No type should be smaller than 6 pt.

TABLES

A maximum of 4 tables is allowed
(This can be modified if needed by Editorial board)

- Tables should be provided as Word files (*.doc) or Illustrator/InDesign (*.ai, *.eps, *.indd) compatible files. No TIFF and JPG files are acceptable for table submission.
- When submitting tables in Microsoft Word table function, no tab, space or colors should be used. Tables should contain a maximum of 10 columns.
- Tables submitted in landscape orientation will not be accepted. Tables should include a title, table legend, and if necessary footnotes.
- Include tables in the submitted manuscript as a separate section.

FIGURE LEGENDS

- Figure legends should be listed one after the other, as part of the text document, separate from the figure files.
- Please do not write a legend below each figure. Each figure legend should have a brief title that describes the entire figure without citing specific panels, followed by a description of each panel, and the symbols used.
- Enough information should be provided in the figure legend text to permit interpretation of figures without reference to the text; but should not contain any details of methods, or exceed 100 words.
- The abbreviated word for figure "Fig." should be typed and bolded, followed by the figure number and a period

(i.e. "Fig. 1."). Every figure legend should have a Title written in bold.
- If a figure contains multiple sections (i.e. A, B, C, D) the letter for these subsections should be in capital letters. Within the figure legend text the capital letters should be surrounded by parenthesis [i.e. (A)(B)(C)(D)].
- Figures should be numbered according to the order of citation.

Supplementary material: Supplementary material, not for review, is acceptable. Supplementary material can be submitted as (*.mov), (*.avi), (*.mpeg), or (*.gif) files. Please note that the size limit for these items is 10 MB per file.

ENGLISH

Authors may be asked to contact professionals regarding the correction of the English content of manuscripts either before or after acceptance. This expense will be the responsibility of the Authors.

C. REVIEW PROCESS

Authors should be aware that manuscripts will be screened upon submission. Only the manuscripts which fully comply with the submission requirements outlined and in which the level of English is of an acceptable standard will enter the peer review process.

First submission

Once successful submission of a manuscript has taken place, an acknowledgement will be sent by e-mail to the Corresponding Author on the manuscript. All subsequent correspondence will be with the designated Corresponding Author. The number of the manuscript should be used by the Authors in all communications with the Editorial Office. All the manuscripts will be reviewed by the Editors and, and in some cases, by other expert reviewers. After review, the corresponding Author will be notified by letter of the decision taken by the Editor(s). This letter will be accompanied in most, but not all, cases by the comments of the reviewers. This letter will be sent via e-mail.

Resubmission of manuscripts

In some cases, Authors will be invited to submit a revised version of the manuscript for further review. This invitation does not imply, in any case, that the revised version will be accepted for publication. In general, revised manuscripts must be received in the Editorial Office within four months of the date of the first decision. Authors should submit the resubmitted manuscript with all changes underlined. The resubmitted manuscript should be accompanied by a cover letter stating that the manuscript has been revised according to the comments made by the Editor and the Reviewers. Figures and tables must be uploaded. Please ensure that a separate point by point response to the reviewers is included with the covering letter. Please do not send revised manuscripts to the Editorial Office via e-mail. Revised manuscripts should mailed to site of Majmaah Journal of Health Sciences at mjhs@mu.edu.sa

PROOFS

Proofs will be made available to the author(s) to be checked. It is the responsibility of the author(s) to make sure that the quality and accuracy of the manuscript, figures, and tables in the proofs is correct. Authors should return their proofs within 48 hours, by fax or e-mail if the corrections are minor, to expedite publication. Further changes or additions to the edited manuscript after these corrections cannot be accepted.

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Cover illustrations will be chosen by the Editors. Authors are highly encouraged to submit high quality color figures and images suitable for publication on the cover at the time of submission of the manuscript.

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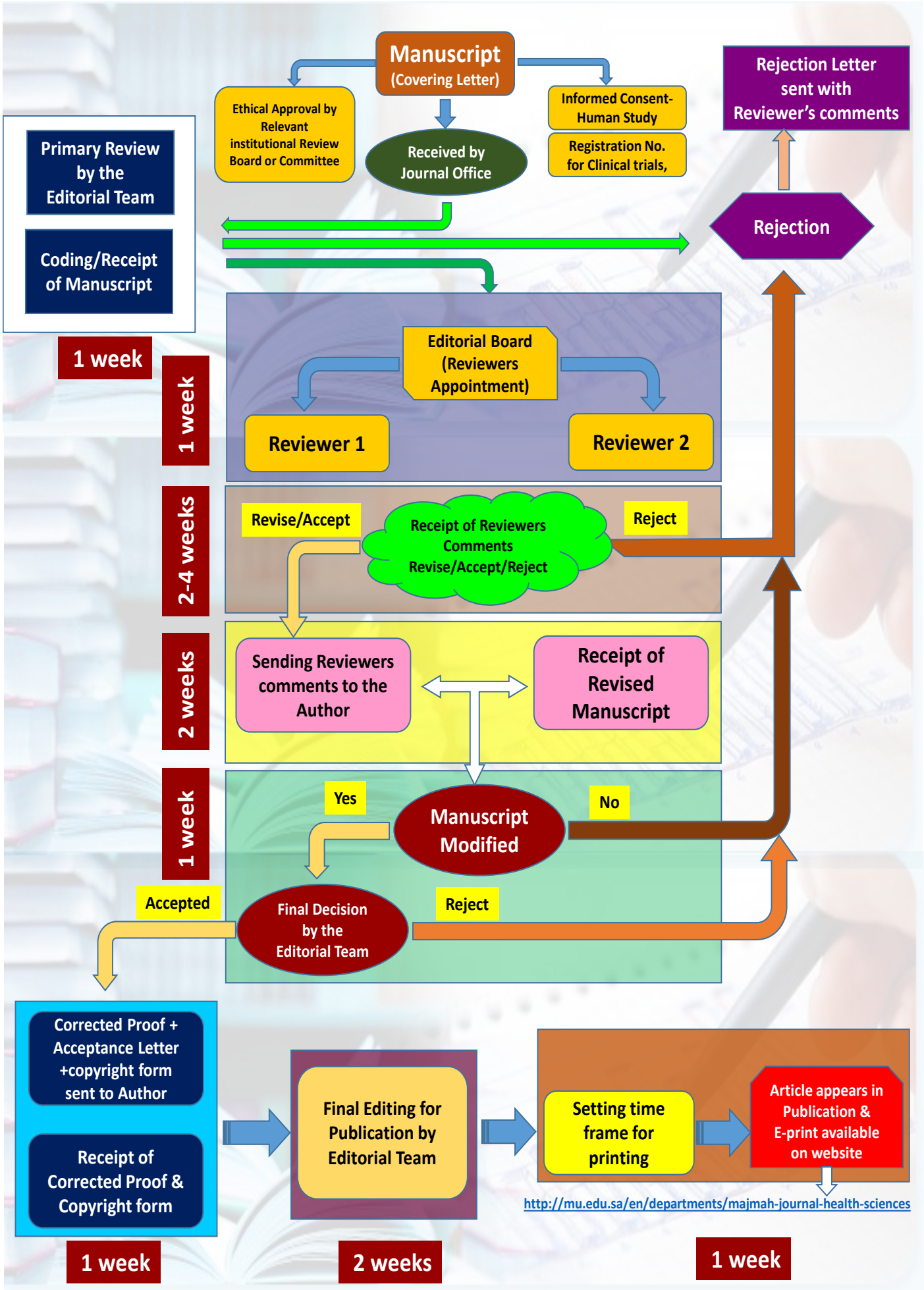
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Drug Declaration/Conflict of Interest Form

This form should be printed out and the suitable statement chosen among the listed ones (A-G). It should then be signed by the corresponding author and faxed to the Editorial Office at +41 22 510 24 00. If this form is not received the paper will NOT be published.

Methodological & Statistical instructions for Authors submitting manuscripts to the Majmaah Journal of Health Science

The manuscripts should include a complete and detailed description of what was done. This includes a description of the design, measurement and collection of data, the study objective and major hypotheses, type and source of subjects, inclusion and exclusion criteria and measures of outcome, number of subjects studied and why this number was chosen. Any deviation from the study protocol should be stated. The baseline characteristics of any compared groups should be described in detail and -if necessary -adjusted for in the analysis of the outcome.

For randomized clinical trials the following should also be clearly documented: treatments, sample size estimation, method of random allocation and measures taken for maintaining its concealment including blinding, numbers treated, followed-up, being withdrawn, dropping out, and having side effects (numbers and type). The statistical methods used should be relevant and clearly stated. Special or complex statistical methods should be explained and referenced.

Complex analyses should be performed with the assistance of a qualified statistician. Unqualified use of such analyses is strongly discouraged. The underlying assumptions of the statistical methods used should be tested to ensure that the assumptions are fulfilled.

For small data sets and if variable distributions are non-normal, distribution free (non-parametric) statistical methods should be used. The actual p values - whether significant or not - should always be presented (not NS). Confidence intervals convey more information than p values and should be presented whenever possible. Continuous variables can always be summarized using the median and range which are therefore preferred. Only in the infrequent case of a Normal distribution are the mean and standard deviation (SD) useful. Complex analyses (including Cox and logistic regression analysis) should be presented in sufficient detail: i.e. variable scoring, regression coefficients, standard errors and any constants. Odds-ratios or relative risks are not sufficient documentation of such analyses. The handling of any missing values in the data should be clearly specified. The number of statistical tests performed should be kept at a minimum to reduce spurious positive results. Explorative (hypothesis generating) analyses without confirmation using independent data are discouraged. Figures showing individual observations e.g. scatter plots are encouraged. Histograms may also be useful. Tables should indicate the number of observations on which each result is being based

UPCOMING CONFERENCES

April 2015

- 07-09 Apr 2015, Dubai World Dermatology & Laser Conference, Dubai, UAE; Organized by the Dubai Derma
- 16-18 Apr 2015, International Conference on Psychiatry Jeddah, Saudi Arabia; Organized by the Saudi German Hospital
- 13-15 Apr 2015, Global Conference on Vaccines, Dubai, UAE
- 15-18 Apr 2015, Annual Arab Heart Congress Cardio Arab, Dubai, UAE
- 29 Apr-02 May 2015, Asian Pacific Society of Cardiology Congress, Abu Dhabi, UAE

May 2015

- May 18-20, 2015, 3rd International Conference on Pediatrics San Antonio, USA
- 01-02 May 2015, GCC Virology Conference, Dubai, UAE
- 22-23 May 2015, Fourth Annual Emirati League Against Epilepsy Congress, Dubai, UAE
- 26-28 May 2015, International Congress On Trauma & Prehospital Care, Dubai, UAE

June 2015

- 8-10 June, International Conference on Flu, 2015 Chicago, USA
- 08-09 Jun 2015 , Clinical Research In Turkey Middle East & North Africa Leaders Forum, Dubai, UAE
- 08-10 Jun 2015, Building Healthcare Exhibition & Conferences, Dubai, UAE

July 2015

- July 20-22, 4th International Conference on Urology, Barcelona, Spain
- July 27-29 4th Asia Pacific Dental and Oral Health Congress Expo, Brisbane, Australia
- July 20-22, 5th Asia-Pacific Summit on Cancer Therapy, Brisbane, Australia
- July 27-29, 4th International Conference and Exhibition on Neurology & Therapeutics, 2015 Rome, Italy

August 2015

- 27-29 Aug 2015, World Congress on Cancer and Prevention Methods, Dubai, UAE
- 2–7 August 2015 Angiogenesis, Newport, United States
- 26–29 August 2015, Rheumatology & Aging Conference, Cambridge, United Kingdom

September 2015

- 01-03 Sep 2015, Saudi International Conference On Scientific Publishing, Riyadh, Saudi Arabia; Organized by the King Saud University
- 28-30 Sep 2015, Global Diabetes Summit and Medicare Expo Dubai, Abu Dhabi, UAE
- 1–3 September 2015, International Conference of Medical and Health Sciences, Yogyakarta, Indonesia
- 3–4 September 2015. 7th International Conference on Ocular Infections, Barcelona, Spain
- 10–12 September 2015, The Viral Hepatitis Congress, Frankfurt am Main, Germany