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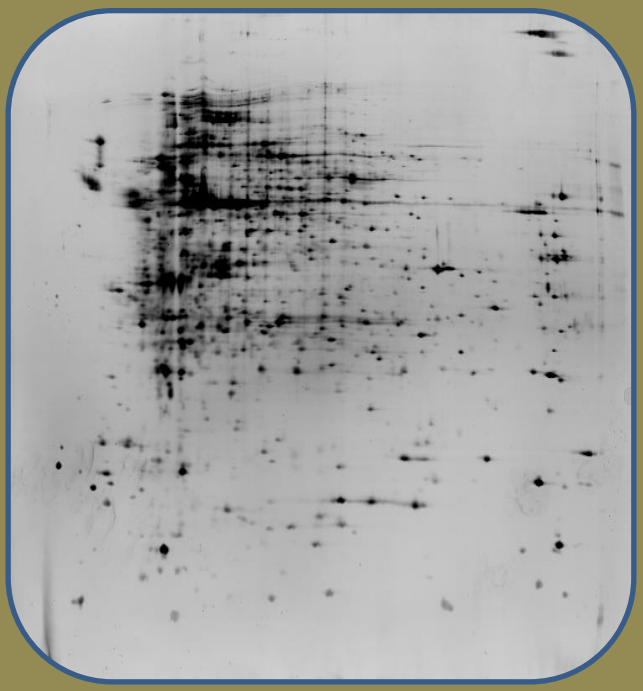

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JUMMEC publishes both basic and applied science as well as clinical research studies on any area of medicine that is of interest and relevance to the medical community. This is a peer-reviewed Journal that publishes twice yearly on Review Articles, Original Articles, Short Communications, Clinico-pathological conference abstracts, Case Reports, Letters to the Editor and Book Reviews.

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We welcome journal submissions throughout the year but preferably by **March** and **September**. Articles submitted for publication are understood to be offered only to *JUMMEC* and which have not been sent to other journals for consideration.

Cover

Image 1) 100ug cMSC - Chondrogenic Multipotent stromal cells 2D SDS PAGE gel profile. Image courtesy of Liang-Xin Tay, Image 2) Say Yes to organ donation- A gift of life. Image courtesy of Lau Yee Ling.

Instructions for Authors

The **Journal of Health and Translational Medicine (JUMMEC)** publishes both basic and applied science as well as clinical research studies on any area of medicine that is of interest and relevance to the medical community. This is a peer-reviewed journal that publishes Reviews Articles, Original Articles, Short Communications, Clinico-pathological Conference Abstracts, Case Reports, Letters to the Editor and Book Reviews.

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Foreword from the Editor

Dear JUMMEC readers,

In present day, researchers and clinicians alike have agreed that science and medicine must work hand-in-hand to face the new dawn of emerging infectious diseases as well as combat the re-emergence of diseases thought to have been put to rest. Scientific research has been proven to play many important roles not only in providing solutions pertaining to diagnosis and treatment of these diseases, but also in developing new and improving existing techniques. Aside from that, in our pursuit of providing adequate healthcare, it is also important that we evaluate current practices held by hospitals around the world for its effectiveness. Thus, medical journals such as JUMMEC play a pivotal role in providing the bridge that connects scientific researchers to clinicians and other researchers working on related field. It is my pleasure to introduce the contributions of a few authors in the fields of Health and Translational Research.

Organ transplantation is a definitive treatment for end-stage organ failure but recent statistics of the number of transplants in Malaysia are dishearteningly low. Thus, Makmor Tumin and his team have contributed two papers on the issue of organ transplantation. The first paper reviews the role of the family in organ transplants and how it influences an individual to sign up as an organ donor. The review highlights that knowledge about brain death and the circumstances surrounding transplantation and organ donation are important factors when discussing organ donation and thus educational efforts should be directed towards families, allowing them to fully understand the process of organ transplantation. The second paper looks at separate opinions on the relationship between brain death and organ donation from the viewpoint of three separate groups of Muslim professionals. Respondents were asked for their opinions on procuring organs from brain dead donors as well as the termination of life support of a brain dead person and the results highlight the importance of education on organ transplantation issues to these groups to allow them to channel their knowledge and perception to the Muslim public.

As mentioned earlier, evaluation of the performance of hospitals is crucial in making sure the public receives the most ideal healthcare. Thus, it is with great interest that we look into the work done by Nabukeera et al in utilising the Pabon Lasso model in evaluating the performance and technical level of hospitals and health centres in Kampala Capital City Authority, Uganda. Hopefully, the Pabon Lasso model may also be utilised in other cities to assess the performance of their respective hospitals and to maintain standards of healthcare in their respective areas.

Also in this issue, a review of current proteomic studies on chondrogenesis by Tay Liang Xin provides knowledge on the recent findings and proteomic approaches utilised in this field of study. Chondrogenic differentiated multipotent mesenchymal stromal cells have shown potential in being used as a treatment for osteoarthritis and thus proteomic studies would allow for a better understanding of the regulating processes of complex mechanisms involved in chondrogenesis.

We would like to thank the readers and contributors to JUMMEC as well as the continued support from the Medical Faculty of University Malaya as this has allowed JUMMEC to continually push forward to provide quality review articles and published material of relevance to local and regional populations. We should promote the journal among both academicians and clinicians to further allow the sharing of knowledge and promote discussion among peers. I would also like to express my special graditute to Prof Atiya Abdul Sallam who has done a great job in managing few articles in this issue.

Lau Yee Ling
Deputy Chief Editor
JUMMEC – the Journal of Health and Translational Medicine

FAMILY DECISION-MAKING ABOUT ORGAN DONATION: A SYSTEMATIC REVIEW

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ABSTRACT

The family is an important factor that influences an individual's decision for organ donation. The number of studies addressing the family's role in organ donation is limited. It is imperative to explore these studies and offer recommendations that may help in addressing organ shortage. 15 studies with more than 2100 participants were selected for a systematic review. The studies were accessed by searching three databases: MEDLINE, Elsevier, and PsycINFO. This systematic review indicates that knowledge about brain death and the circumstances surrounding organ donation and transplantation are the most important factors that affect a family's decision regarding organ donation. Educational efforts targeting the family should be initiated, which can then guide the family's decision on organ donation. We suggest that educational efforts be consistent with other factors such as religious beliefs that influence the family's decision.

Keywords: *deceased donation, family decision, family education, living donation, organ donation*

Introduction

Many factors are considered when an individual is making a decision on organ donation. A systematic review of 18 studies involving 1,019 participants revealed that there are eight main factors that influence an individual's decision regarding organ donation. They are relational ties, religious beliefs, cultural influences, family influences, body integrity, interaction with the health-care system, knowledge about organ donation, and reservations about the process of organ donation (1).

Of these eight factors, the family is the most important. It is universally accepted that the family is responsible for shaping an individual's ethical considerations. Consequently, it can have a bearing on a person's willingness to donate organs. There have been only a very limited number of studies focusing on the family as the fundamental decision-making institution on organ donation. This paper aims to examine how the family institution plays a role in influencing the decision to donate organs.

There are three main reasons why we should focus on providing the family with information on organ donation if we are to improve organ donation. Firstly, the family can influence an individual to become a related living organ donor. Families are genetically and emotionally related to the patient, and they are often referred as potential donors before an appeal for organ donation is made to the public. Secondly, the family can provide the ethical basis and influence on an individual's decision to donate organs. The family, for instance, can influence the individual to sign up for organ donation. Thirdly, the family plays a major role in deciding on deceased organ donation. In this context, the family is the final decision maker and have the legal right to overrule the consent of the deceased for organ donation made whist still living. This is the legal procedure in most of the countries with organ donation systems (2). In Malaysia, for instance, the Human Tissue Act 1974 stipulates that the family's consent has to be taken before procuring organ(s) from the body of their loved ones, even when the deceased had registered to donate his organs before his death.

Taking into account the above arguments, it is thus imperative that we analyze the literature on the influence of the family in organ donation. Three things are of interest to us. We would like to identify from the literature the various factors that determine families' decision about encouraging living related organ donation. We would also like to examine the significance of the role various family members play in allowing relatives to pledge for organ donation. Finally, we would like to locate in the literature

the factors that could contribute to a family's willingness to give consent to donate their relative's deceased organs. By focusing on these three issues, we hope that this systematic review will shed further light on the direct and indirect impact of the family on organ donation. The direct impact comes from the family role in allowing organs to be harvested from the deceased family member, while the indirect impact stems from the family's influence on the individual's decision to become an organ donor.

Methods

We reviewed and summarized 15 journal articles. We focused on three themes that were of concern to us. The first involved factors that influence a family's decision to encourage living related organ donation. There were seven studies, with more than 4,000 participants. The second concern involved factors that influenced families' decision to allow relatives to become organ donors. We identified two papers, with views from 155 respondents. The third concern involved factors that influenced families' consenting to deceased organ donation. We chose three articles with views from 550 respondents.

The articles were selected from three online databases, namely, MEDLINE, Elsevier, and PsycINFO. We used keywords such as "organ," "deceased donation," "living related," and "family influence" in order to retrieve relevant studies for each of the themes.

Results

As mentioned in the Methods section, we divided the literature into three groups based on factors influencing a family's decision about organ donation: becoming living donors, allowing a relative's pledge for organ donation, and allowing a deceased relative's organ donation.

(i) Becoming living donors

Previous studies looking at the family's role in influencing the decision to become a living donor can be grouped into emotional and nonemotional factors. In a literature review, Conrad and Murray (3) found that kidney recipient's emotional outlook is critical in determining the family's ability to influence living related organ donation. They concluded that kidney recipient's negative feelings and expressions played an important role in the family's ability to encourage living related organ donation.

Stothers *et al.*'s (4) study on 27 previous living donors and 387 relatives of patients listed on waiting lists for organs discovered that the ability of families to encourage living related organ donation could be due to pressure from constant requests. Pressures are often felt by would-be organ donors when family members or medical professionals made direct requests for living donation to the potential donor. Approximately 4% of living donors cited family pressure as the reason for them making an organ donation (4). Jacobs *et al.*'s (5) analysis of 524 previous living donors' responses revealed that the donors were more likely to feel pressured to donate if the recipient were a sibling or an offspring.

Rodrigue and Guenther's (5) review of the psychology of live liver donors found emotional concerns as the main factor influencing family members to agree on living organ donation, where the emotional links with the recipient often encouraged families to save or improve the quality of their loved one's life. Potential donors were also inspired to become living related organ donors because of feelings of responsibility, duty, or internal pressure to do the morally correct thing for their family members.

Some studies found that nonemotional rather than emotional factors influenced the decision on living organ donation. Lee *et al*. (7) concluded that knowledge of organ donation and transplantation determined the likelihood of family member to become a living donor. Their research collected responses from 209 individuals and found that the lack of knowledge about organ donation was one of the most important factors that discouraged one from being a living related donor. About 42% of the respondents, who had hesitated to donate (92 of 209 respondents) cited that the lack of information was a source of anxiety for them when deciding to donate their organs. The other reasons revealed by respondents that were indirectly related to the lack of knowledge of organ donation were the fear of pain and complications, death after surgery, and the inability to maintain a normal life after donation.

Another study cited the age of the family members as a determining factor in an individual's willingness to be living organ donor. Yang *et al*. (8) looked at the case of living organ donation in China for 302 family members of kidney failure patients. They found that the attitudes toward living related kidney donation were highly influenced by nonemotional factors, for instance the age of the family members. The study found that the respondents who were 45 years old and above were more in favor of organ donation than those aged 35 years and below. Besides the age of the potential donor, Yang *et al*. also confirmed Lee *et al.*'s results on the importance of knowledge of organ donation as a determinant of the willingness regarding living donation.

(ii) Allowing a relative's pledge for organ donation

Getting the family to understand organ donation is an important avenue to encourage organ donation from related members of the family. Various studies have reported that some individuals abstained from being organ donors merely because they failed to obtain permission from family members. A study on the attitudes of 141 Muslim Indo-Asians in West London toward transplantation in the United Kingdom found that most of the participants did not allow their children to obtain a donor card (9). One of the female respondents in the study stated that she had no objection in donating her organs, unlike her father who objected to her decision on donating organs. Another female respondent stated that she could not decide on the donation because it required permission from her husband. A study by Morgan *et al*. on 14 men and women

of Caribbean descent, living in South London, reported that the fear brought about by the family members about body integrity and the thought of the body being "cut up" were some of the reasons why individuals chose not to support their relatives becoming donors (10).

(iii) Allowing deceased relative's organ donation

Three studies suggested that there were modifiable factors, which, if properly handled, could lead to families giving consent for deceased organ donation. The review of Simpkin *et al*. of 20 selected studies pertaining to alterable factors that influenced a family's decision on organ donation suggested three main factors. The first factor was inadequate knowledge of organ donation and brain death; the second was the process of requesting consent, the "who, when, and where" to request the consent; and finally, the effect on the prospective donor's health (11). In this context, Orøy *et al.*'s interviews with 16 nurses, 12 physicians, and 4 hospital chaplains concluded that the main problem faced in delivering the message of organ procurement from a deceased donor was choosing the most appropriate time to raise the issue to the deceased's family (12).

Ghorbani *et al*. (13) reported on the causes of family's refusal for organ donation and found that the poor acceptance of brain death was the major reason for a family to refuse organ donation. The study, which was conducted on 81 families of potential organ donors who had refused organ donation, found that 44.4% of the families indicated that uncertainty of the brain death circumstances was one of the reasons for not allowing deceased organ donation by their family members. Other factors such as unknown donor wishes and religious issues were also stated as leading reasons toward family's objection to deceased organ donation.

Organ trading has become a global concern in the last few decades, and many regulations have been introduced to fight this unethical practice in many countries. Families feared that their loved ones' organs—if they consent to donate—would not be used legally and ethically and have refused organ donation. Ghorbani *et al*. found that 9.9% of families refused to donate their love ones' organs due to fear of organ sale (13).

Siminoff *et al*.'s study on 49 family members pointed out that there were other reasons for a family's disapproval of deceased organ donation. These reasons included families' lack of knowledge of the deceased's organ donation wishes, family members' lack of knowledge about the extent of the patient's brain injury, and the inability of medical professionals to clearly communicate to the family members on the extent of the patient's brain injury (14). Another study on 420 cases of deceased organ donation decision-making also revealed that communication among family members on organ donation was an important criterion, which influenced family members' decision to allow for deceased organ donation. The study found that families that conducted frequent conversations on organ donation were more likely to donate (15).

Discussion

This paper sets out to look at the influence of the family in determining organ donation. The family factor of organ donation is discussed from three aspects: encouraging related living donation, allowing a family member to pledge to donate organs after death, and consenting to deceased organ donation. In a collective point of view of the three aspects, we found from the literature that there are various factors that can influence a family's decision on organ donation. The factors can be categorized based on their importance as noted in the literature. In this context, knowledge about organ donation and transplantation and the pertinent circumstances surrounding them have been most cited among the studies reviewed in this paper, to affect all three themes discussed in this paper. This highlights the vital role of family education on organ donation and transplantation in influencing the rate of deceased and living organ donations.

Emotional factors, including the feelings of sympathy toward a family member who is in need of an organ, also play a crucial role in determining the willingness of an individual to become a living donor, especially among relatives. There are many other factors cited in the literature influencing the family's decision regarding organ donation, such as the procedure/process of getting consent from the family members in the case of deceased donation, the fear of organ trading, religion-related matters, and others. The analysis of the literature puts family education central in any initiative to increase organ donation rates. Future studies should be focused on methods of delivering information to families, to enable them to resolve their organ donation issues (see Table 1).

Table 1: Factors influencing family decision on living and deceased organ donation.

Factor	Study
Knowledge about brain death and organ donation and transplantation.	(7), (11), (13), and (14)
Emotional factors	(2), (3), (4), (5), and (6)
Others	
The request process of organ procurement	(12) and (13)
Body integrity	(1), (10), and (13)
Fear of organ trading	(11)
Religious matters	(11)
Communication among family members	(15)
Donor's age	(8)

This paper provides a precise summary of recent literature findings on family's decision making on organ donation. The studies included in this article were randomly selected from the limited number of available studies pertaining to the scope of this research. A wider systematic search of the literature may provide a more comprehensive review on this topic. We believe however that our review provides important guidelines for future research in this area.

Conclusion

We conclude that the improvement of organ donation rates through the family channel requires adequate and appropriate efforts to educate people about organ donation and transplantation, especially on brain death and the circumstances surrounding the issue. The lack of knowledge is the factor which may impede organ donation, whether living or deceased. In the case of living donation, more often than not, emotional factors influence not only an individual to become an organ donor but also a family's decision to put pressure on the prospective donor. However, the review suggests that emotional factors must be complemented by knowledge of living donation.

In the case of deceased organ donation, it is most important to educate the family members about the definition and condition of brain death, besides disseminating information regarding organ donation, such as body integrity, religious acceptance toward organ donation, as well as the process of organ procurement. Choosing the right time to request the family's consent to donate their loved ones' organs is crucial in this context.

Given our understanding of the importance of knowledge in influencing a family's decision and acceptance toward organ donation, it is of fundamental concern to tackle the issue of dispersing information to the family members. We suggest that future studies focus on answering the question of "what are the appropriate educational methods to enhance family knowledge about organ donation and transplantation?"

Acknowledgments

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BRAIN DEATH AND ORGAN DONATION: A COMPARISON OF THREE INFLUENTIAL GROUPS OF MUSLIM PROFESSIONALS

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ABSTRACT

Organ transplantation is a new treatment for end-stage organ failure. However, the total number of transplants performed in Malaysia in 2012 was only 94. Rates of deceased and living donors in Malaysia for 2012 were chronically low (0.55 and 1.87 per million population, respectively). A sample of 350 respondents in mosques, hospitals, and universities in various places in the Klang Valley, Kelantan and Pahang were collected between October and December 2013 to investigate the level of knowledge of health care professionals (HCPs), religious leaders (RLs), and academics (ACAs) and their stand on two issues on brain death. The result on the first issue (procuring organs from brain dead donors for transplantation) revealed that 52.8%, 23.7%, and 23.4% of HCPs, RLs, and ACAs, respectively, were in support of it; 30.2%, 31.8%, and 45.2% were uncertain about it; and 17%, 44.5%, and 31.5% were against it. On the second issue (terminating the life support machine of a brain dead person), 60.4%, 35.7%, and 25% of HCPs, RLs, and ACAs, respectively, were in support of it; 26.4%, 36.4%, and 38.7% were uncertain about it; and 13.2%, 27.7%, and 36.3% were against it. The lack of knowledge on Islam brain death-related issues should be addressed by educational efforts targeting these three groups of professionals. Special emphasis should be paid to educating RLs as they can channel their knowledge and perception to the other groups and to the Muslim public.

Keywords**:** *brain death, knowledge, Malaysia, Muslim, organ donation*

Introduction

Rapid medical progress has introduced organ transplantation as a new treatment for end-stage organ failure. The success of this new treatment depends vitally on the availability of donated organs. However, many countries around the globe have faced a severe organ shortfall, impeding the treatment of thousands of patients needing an organ transplant. In Malaysia, the number of dialysis patients in 2012 was 28,590, with about half registered on the waiting list for a renal transplantation; however, the total number of transplants performed in that year was only 94 (1,2). The major cause of this discrepancy was that rates of deceased and living donors in Malaysia for 2012 were chronically low (0.55 and 1.87 per million population, respectively) compared with other countries in the developed and developing world, such as Spain (35.12, 8.59), the United Kingdom (20.7, 17.8), Iran (8.7, 20), Turkey (5.0, 46.6), Kuwait (3.7, 16.7), and Saudi Arabia (2.5, 24.7) (3).

To address the dilemma of organ shortage, many studies have investigated factors affecting organ donation. Most such studies emphasise the importance of knowledge on organ donation and transplantation in determining willingness to donate organs (4–10). On the other hand, many authors have also identified the role of religion in guiding people's viewpoints and attitude toward organ donation (7,11–1Generally, people become more willing to donate when they know that religious leaders (RLs) support organ donation (15). Muslim scholars or RLs are responsible for making Islamic rulings about contemporary issues and advising the Muslim public on those issues. The role of RLs is thus vital in driving up donation rates (15–18). In Turkey, a study showed that about 50% of Muslim RLs had been

consulted on organ donation issues (11). In Malaysia, 84% of Muslim health care professionals (HCPs) admit that RLs play an imperative role in educating the public on organ donation (19). Another study in Malaysia has shown that RLs are the second most preferred promoter of organ donation (20).

The knowledge and attitude of HCPs toward organ donation and brain death is of great importance, since they are in direct contact with patients and their families, who are potential organ donors. In this context, many studies have found a relationship between training HCPs on organ donation and organ donation rates (21,22). A study in Turkey concluded that a lack of knowledge on organ donation has negative effects on HCPs' views toward organ donation. Another study found that 28.7% of Turkish HCPs do not donate their organs due to their Islamic religious beliefs (8). A recent study in Malaysia showed that willingness to donate organs is lowest among Muslim HCPs (37.3%) compared with those of other religions. The study suggested that the misconception among HCPs about brain death is a significant reason impeding HCPs' abilities to identify organ donors, and, thus, undermining donation rates (19).

Academics (ACAs) are presumed to have a great deal of influence through either teaching in universities or conducting research and proposing policies that shape the destiny of their communities. Unfortunately, no study has thus far been conducted to explore ACAs' viewpoints and attitude toward organ donation and brain death. Moreover, to the best of our knowledge, no study has been conducted on Malaysian RLs' perception and knowledge on the issue of organ donation and brain death or on the permissibility of procuring organs from a brain dead donor. This is imperative given the knowledge and perception of Muslim HCPs and ACAs, and is thus the aim of this study.

Methods

A survey was conducted in different areas for different sample groups. RLs' sample was based on 82 mosques in the Klang Valley. HCPs' sample was based on 3 hospitals; University Malaya Medical Centre (33), Hospital Raja Perempuan Zainab II (10), and Hospital Tengku Ampuan Afzan (10). ACAs' sample was collected from 3 universities in the Klang Valley; University of Malaya, Universiti Sains Islam Malaysia (USIM), and Universiti Teknologi MARA (UiTM) Shah Alam. The study was approved by the University of Malaya Research Ethics Committee (Reference Number: UM.TNC2/RC/H&E/UMREC).

Enumerators were trained to approach HCPs, RLs, and ACAs in their respective locations and obtained respondents' verbal consent before proceeding with the survey. Self-administered and pilot-tested questionnaires were handed over to respondents. In the survey, 53 HCPs, 173 RLs, and 124 ACAs, totalling 350 respondents, participated; all respondents were Muslims.

An RL in this survey is understood as (i) an individual with an Islamic educational background and/or (ii) an active member of a local mosque's committee. Academics who have an Islamic background and are also a part of the mosque committee are grouped under RLs in this study.

After completing the demographic section of the questionnaire, respondents were asked to answer the question: "Are you willing to become a donor upon death?" They were presented with two options, "Yes" or "No". This question is important to examine their overall attitude toward being deceased donors. Next, to examine their level of knowledge, the following seven questions of common knowledge were presented to them with the same "Yes" or "No" options:

1. Healthy individuals can lead a normal life with one kidney.
2. Organs from deceased donors can be retrieved even without the donor's family's consent.
3. A person is actually dead if his/her brain has stopped functioning, even though his/her heart is still beating with the aid of a machine.
4. Living donors can lead a normal life without medication.
5. An organ donated by a Malay, Chinese, Indian, or a person from other ethnic groups would only be transplanted to a patient of the same ethnicity.
6. Registering with a medical officer is the only way to become a deceased donor.
7. Fatwa (Islamic ruling) in Malaysia allows organ donation.

Respondents' level of knowledge was divided into three groups based on their correct answers: poor, 2 and below; moderate, 3 to 4; and good, 5 to 7. Finally, their views on two issues related to brain death were recorded. The issues were "Removing organs from brain dead patients for transplant purposes is permissible in Islam" and "Switching off the mechanical ventilator for brain dead patients is permissible in Islam". A five-point Likert scale was used to determine the score for each item (strongly disagree, disagree, not sure, agree, strongly agree). Respondents' attitude were divided into 3 groups; support (respondents that strongly agree and agree), uncertain (respondents that are not sure), and against (respondents that strongly disagree and disagree). The questionnaires were distributed in Bahasa Melayu.

Results

The results of the surveys indicate that of the 350 respondents, 220 (62.9%) are willing donors. From these numbers, 16.4% willing donors are HCPs, 49.5% RLs, and 34.1% ACAs.

Table 1 presents respondents' demographic and socioeconomic characteristics

The overall background of the three group of respondents is as follows; Out of 350 respondents, 237 (67.7%) were male. 28.3% of the respondents were aged 35 years and below, 54.3% were aged 36 to 50 years, while the remaining

Table 1: Respondents' Background

Respondents' Background	HCP* (n=53)	RL** (n=173)	Aca*** (n=124)	Total (n=350)
Gender				
Male	20	130	87	237
Female	33	43	37	113
Age				
35 years and below	28	44	27	99
36 to 50 years old	24	91	75	190
51 years old and above	1	38	22	61
Income				
RM 2,000 and below	0	79	0	79
RM 2,001 to RM 4,000	0	67	0	67
RM 4,001 to RM 6,000	15	18	71	101
RM 6,001 to RM 8,000	12	4	17	33
RM 8,001 to RM 10,000	6	4	24	34
RM 10,00 and above	20	1	12	33
Education Background				
Conventional education	48	115	124	287
Islamic education	5	58	0	63
Highest Education				
School and Undergraduate Level	0	166	0	168
Postgraduate level	53	7	124	181
Field of knowledge (respondents with higher education only)				
Medical science	53	0	0	53
Non-medical science	0	3	17	20
Social science/Islamic studies	0	18	107	125
Mosque committee				
Yes	3	1550	37	195

*HCP - Health Care Professionals

** RL - Religious Leaders

***Aca – Academicians

Table 2: Respondents' Level of Knowledge (general information) on Organ Donation and Transplantation

Level	HCP* (n=53)	%	RL** (n=173)	%	Aca*** (n=124)	%	Total (n=350)	%
Poor	2	3.8	50	28.9	21	16.9	73	20.9
Moderate	28	52.8	103	59.5	79	63.7	210	60.0
Good	23	43.4	20	11.6	24	19.4	67	19.1

*HCP - Health Care Professionals

**RL - Religious Leaders

***Aca – Academicians

Table 3: Respondents' Perspective on Brain Death and Organ Donation from an Islamic Standpoint

Variables	**Response**	**HCP* (n=53)**	**%**	**RL** (n=173)**	**%**	**Aca*** (n=124)**	**%**	**Total (n=350)**	**%**
Removing organs from brain dead for transplant purposes is permissible in Islam	Strongly Disagree	2	3.8	17	9.8	10	8.1	29	8.3
	Disagree	7	13.2	60	34.7	29	23.4	96	27.4
	Not sure	16	30.2	55	31.8	56	45.2	127	36.3
	Agree	19	35.8	26	15.0	25	20.2	70	20.0
	Strongly Agree	9	17.0	15	8.7	4	3.2	28	8.0
Switching off the mechanical ventilator for brain dead patients is permissible in Islam	Strongly Disagree	3	5.7	16	9.2	10	8.1	29	8.3
	Disagree	4	7.5	32	18.5	35	28.2	71	20.3
	Not sure	14	26.4	63	36.4	48	38.7	125	35.7
	Agree	25	47.2	39	22.4	24	19.4	88	25.1
	Strongly Agree	7	13.2	23	13.3	7	5.6	37	10.6

*HCP - Health Care Professionals

**RL - Religious Leaders

***Aca – Academicians

17.4% were aged 51 years and above. Based on income, 79 (22.6%) had incomes of RM2000 and below, 67 (19.1%) had incomes of RM2001-RM4000, 101 (28.9%) had incomes of RM4001-RM6000, 33 (9.4%) had incomes of RM6001-RM8000, 34 (9.7%) had incomes of RM8001-RM10000; and finally, 33 (9.4%) had incomes above RM10000. 287 (82%) of the respondents had conventional education while the remaining 63 (18%) went through Islamic education. Based on highest education, 168 (48%) reached school and undergraduate level, while the remaining 181 (52%) reached postgraduate level. 53 (15.1%) of respondents were medical science based, 20 (5.7%) were non-medical science based, while 125 (35.7%) went through Islamic studies and social science studies. The remaining 43.5% of the respondents did not have higher education.

Table 2 indicates that RLs' level of knowledge on organ donation and transplantation is the lowest compared with ACAs, while the level of knowledge of HCPs is the highest. Only 11.6% of RLs have good knowledge on organ donation compared with 19.4% of ACAs and 43.4% of HCPs.

Table 3 indicates that more than one third of respondents are unsure that "Switching off the mechanical ventilator for brain dead patients is permissible in Islam". ACAs were the least knowledgeable on this issue, while HCPs were the most knowledgeable. In other words, the majority of HCPs (60.4%) support that brain death criteria comply with Islamic teachings on death, while only 35.7% of RLs and 25% of ACAs support this notion.

The three groups' support for the second issue related to brain death is slightly lower compared with the first. Only 52.8%, 23.7%, and 23.4% of HCPs, RLs, and ACAs, respectively, side with removing organs from brain dead patients for transplant purposes. On the same matter, a sizable portion of HCPs (30.2%), RLs (31.8%), and ACAs (45.2%) are uncertain, as shown in Table 3.

Discussion and Conclusion

Malaysia is a multi-ethnic country with three chief ethnic groups: Malay (50.1%), Chinese (22.6%), and Indian (6.7%). Four main religions prevail in the country: Islam (61.3%), Buddhism (19.8%), Christianity (9.2%), and Hinduism (6.3%) (23). Becoming an organ donor in Malaysia requires the willing donor to register his/her wish officially. Registration can be performed easily online through a user-friendly website (http://www.dermaorgan.gov.my)(24).

Generally, most religions permit organ donation and transplantation (12). As for Islam, the majority of Muslim scholars or RLs permit organ donation as a form of charity (16,25–28). In Malaysia, organ donation and transplantation have been recognised and permitted by the National Fatwa Council since 1970. The official Islamic verdict in Malaysia also allows cross-religion and cross-ethnic organ donation and transplantation (24).Organs can be procured from a cadaver or a brain dead donor; however, in most countries, most organs for transplantation are sourced from brain dead donors owing to viability constraints(29).

Muslim scholars have been in controversial deliberations about the definition of death, which is a vital factor to determine donated organs. The traditional definition of death in Islam is "the departure of the soul from the body". Derived from the primary source of Islamic jurisprudence – Quran and Hadith – this definition is vague and does not provide a clear illustration of the signs of soul departure (30).

Medical advancement has led to a new definition of death, "brain death", introduced in 1968 by a group of scholars from Harvard Medical School. In their words, brain death is an "irreversible cessation of function of the entire brain" (31). Accordingly, Muslim scholars have been urged to determine whether the new definition of death complies with Islamic teachings. However, consensus on the issue of brain death among Muslim scholars remains lacking. Nevertheless, the majority of Islamic rulings and the verdict of important bodies in the Muslim world, such as the Islamic Fiqh Academy (1988) and Islamic Organization for Medical Sciences (1985), have approved brain death as the modern medical sign of death (32,33).

Earlier studies found that the lack of information on organ donation and transplantation caused the Malaysian public to be unwilling to donate (6,34). Although knowledge on organ donation should not be low among people with higher levels of education, surprisingly, this study shows that the three professional groups investigated in this work – HCPs, RLs, and ACAs – lack adequate knowledge on the basic issues of organ donation and transplantation, with RLs showing the worst level of understanding.

The absence of adequate knowledge among the studied groups is extended – by the findings of this study – to cover the permissibility of terminating the life support machines of brain dead patients, and, hence, the permissibility of procuring organs from brain dead persons for transplantation purposes.

The lack of knowledge is rather chronic among RLs, although they are expected to be more exposed to Islamic contemporary fatwas in the country. This finding indicates that the new definition of death introduced in 1968 by Harvard medical experts and approved in 1992 by Muslim officials has not been promoted properly among the three groups in this study, especially RLs who are expected to play a vital role in channelling information on organ donation to Malaysian Muslim communities(19,20).

The role of HCPs is very significant in organ donation. HCPs are responsible for declaring the death of a patient, contacting an organ donation coordinator, and approaching families of prospective donors to obtain their consent to procure his/her organs(19,21). Thus, HCPs are undoubtedly a key determinant of organ donation rates. Ethical concerns among HCPs are determined within their cultural frames besides their theological beliefs. The theological concerns of HCPs may lead to the acceptance or rejection of organ donation (8). Therefore, a lack of knowledge among HCPs on organ donation and brain death – connected

with their theological beliefs – means the severe failure to procure donated organs for transplantation(21,22). Thus, the relatively low level of knowledge among HCPs shown in this study is a serious problem that needs to be addressed urgently to increase awareness on the issue of organ donation.

The inclusion of ACAs in this study provides us with two important elements. The first is to gauge their views on the issues searched, as ACAs are deemed to influence the nation's future. The second is to provide an unbiased benchmark when comparing RLs and HCPs, since the topic investigated is medical-religious-oriented. As a result, this study reveals that ACAs exhibit the least acceptance and highest uncertainty about issues pertaining to brain death among the three groups. The comparison presented herein shows a wide gap between HCPs and RLs in terms of knowledge on the Islamic view of brain death issues. For instance, 52.8% of HCPs agree that removing organs from brain dead donors is permissible in Islam compared with 23.7% of RLs and 23.4% of ACAs.

The ambiguity and misconception among Islamic perspectives on brain death urge educational initiatives aiming to increase awareness of the Islamic permissibility of announcing brain dead patients as deceased and procuring their organs. These would enhance the number of approached donors and thus the number of organ transplantations in the country.

The need for educational efforts on brain death should intensively target RLs for three reasons. The first is that their level of knowledge on Islam brain death matters is very low. The second is that RLs can influence the public's perception of organ donation more than other professional groups. The third is that RLs can serve as a reference of knowledge for HCPs and ACAs when they seek information on the Islamic perspective of brain death. Such an argument is supported by the recent findings that show that about 84% of Malaysian Muslim HCPs stress the important role of RLs in raising the awareness of and promoting organ donation(19).

This study has some limitations. It only covered the Klang Valley, and 2 hospitals in Kuantan, Pahang and Kota Bharu, Kelantan; thus, generalising the findings may suffer some bias. However, we argue that the demographic and urban characteristics of these areas mirror the components of the Malaysian Muslim community, by and large. Another limitation is that the number of HCPs is much lower than the participants from other groups. Nevertheless, we believe that the samples roughly portray the relative formation of the three professions in the country.

Our analysis of 53 HCPs, 173 RLs, and 124 ACAs reveals that they lack adequate knowledge on the Islamic stance on brain death and the permissibility of procuring organs from brain dead donors. This lack of knowledge may have been undermining organ donation and transplantation activities in Malaysia, as brain dead donors are the ultimate source of organs. An educational strategy should be taken into account to address this deficit in information. We suggest that RLs need this education the most as key players in determining organ donation status in the Islamic community.

Limitations and Future Studies

This study was based on participants from 3 medical centres and 3 universities. The views of HCPs and ACAs in other institutions might be slightly different. In addition, the study did not investigate within-group differences because it initially aimed to compare influential groups (HCPs, RLs, and ACAs) without within-group settings. Future studies may cover a larger number of medical and academic institutions and may include within-group analysis.

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AN EVALUATION OF HEALTH CENTERS AND HOSPITAL EFFICIENCY IN KAMPALA CAPITAL CITY AUTHORITY UGANDA; USING PABON LASSO TECHNIQUE

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ABSTRACT

The Pabon Lasso Model is one of the most important and suitable techniques applied in evaluating the performance of hospitals. The visual representation standardizes the comparative accomplishments of hospitals which information is used by planners in effort to improve productivity of the health care system by use of three pointers namely: (i) Average Length of Stay (ALS); (ii) Bed Occupancy Rate (BOR); (iii) Bed Turnover (BTO). The purpose of this study is to evaluate performance of wards in health centers affiliated to Kampala Capital City Authority (KCCA) and Ministry of Health (MOH) during the financial year 2012-2013 constructed on Pabon Lasso Model. Data for the nine health centers and two referral hospitals was taken by the nursing sisters who were in charge. To ensure accuracy, a weekly standard report was submitted to head office and the data included: a list of wards, number of beds, admissions, deaths, discharges and inpatient days. For all government health centers and hospitals, overall, the average indicators ALS=3.63 days, BTO= 74.0 times per year and BOR=49.3% were obtained. Based on the Pabon Lasso graph, two wards are in Zone 3, two wards in Zone 4, one ward in Zone 2 and five wards in Zone 1. The performance of health centers and hospitals in Kampala were somehow poor. This represented unacceptable levels of technical deficiency.

Keywords: *Efficiency, Pabon Lasso, health centers, hospitals, Uganda*

Introduction

Public health centers perform a significant role in the health care structures. These are health center establishments that possess a structured medical and other specialized staff. They provide medical related services in a varying range and in doing so, they create vital data for research, learning and administration (1).

For the past two decades, the government of Uganda significantly appreciated the need for improvement in health infrastructure expansion, human resource training, welfare improvement and health policies, procedures and guidelines (2, 3, 4). Health Infrastructure development of health centers, laboratories and theaters were to improve quality and service equity (4).

However, regardless of efforts of establishments by the authorities, health care worker providers, traditionally oriented challenges related to practical professional inefficiencies, unmet demands, limited resources, public-private partnerships, donor funding, existing arrangements, scarce specialists, equitable distribution and unfortunate welfare of health workers pose major challenges to policy makers in Uganda (5, 6, 7) as well as at the global level (8, 9, 10). Approximately all health centers I, II, III and IV in Uganda still encounter unmet expectations though services delivered entirely depend on the status awarded. What remains uncertain is the performance of health centers in these circumstances and important factors to enable them survive the test of time.

Ministry of Health and medical researchers in Uganda have acknowledged parallel difficulties which further threaten hospitals from contributing to healthier population. These include: collapsed referral system, insufficient funding for necessary expenditures like ambulance fuel and maintenance, increased pressure for quality services, delayed supplies of blood in addition to poor road networks in the areas and absence of emergency medicines, workforce shortage, failures in task shifting,

inequality in health with bias to the disadvantaged, delayed care seeking, failure or delay to reach the health center, delayed institutional care, increasing demand health services (11, 12).

Usually, given such circumstances, economy, equity, effectiveness, standards, quality, quantity and safety are largely ignored or marginalized. It is essential for administrators, decision-makers and policy makers to evaluate and monitor the performance of health centers' present status and services delivered, to utilize the available resources efficiently, to withstand and enhance a health population in spite of the constraints.

Available evidence shows that current escalated economic burden on public health centers has been met by the victims. World Bank reports indicate that health centers are increasingly allotted a sizeable portion of resources for health expenditure in developing countries (13) while the least for poor developing countries (1). Uganda's total expenditure on healthiness as a percentage of total state expenditure has risen from 7.3% in 2000 to 13.6% in 2009 (1) but there is no factual proof that the increase in health expenditure has better outcomes on healthcare. While there is lack of evidence, the mixture of private not for profit (PNFP) and private health practitioners are also competing at the same space and performing better than the government health centers (7) though their costs are high in a country without government health insurance. Though there are free health services in health centers (14, 15, 16), quality is still lacking (17, 18).

Bearing in mind the above stated concerns, it is significant to consider the performance yardsticks of health centers in order to advise interested parties well on the issue that has been essentially disregarded. Ugandan Ministry of Health (MOH) has categorized selected Efficiency Parameters 2011/12 (2) as shown in Table 1.

Table 1: Annual Health Sector Performance Report 2011/2012

Yardsticks	Average	Minimum	Maximum
Average Length of stay	5.48	0.59	12.05
Bed-Turn Over rate	63.5	76.19	78.85
Bed occupancy Rate (%)	96.89	6.74	235.35

Methodology

To date, many methodologies, methods, illustrations and models have been offered to assess the performance of health centers better and gauge their productivity, financing, distribution and utilization of scarce resources as means to control their inefficiencies (19, 20). This significant and helpful model for assessment of health center accomplishments is Pabon Lasso Model. It was initiated in 1986 by Pabon Lasso for usage in ascertaining the comparative accomplishments of health centers and it has proved one of the greatest model, valued for comparing the different hospitals or diverse units inside the health centers using three yardsticks namely: average length of stay [ALS]; bed turnover rate [BTO]; and bed occupancy rate [BOR] to make up the overall assessment of performance (21). Understanding of accomplishments by the use of this model is constructed on a chat split into four fixings depending on the average measures:

(i) Wards having low-level BTO and low-level BOR point out an extra of hospital beds compared to the present requirement (Zone 1).

(ii) Wards with high-level BTO and low-level BOR (Zone 2) characterized by unwarranted hospitalized patients and excess bed capacity or bed usage for just detecting patients.

(iii) High-level BTO and High-level BOR (Zone 3) characterize wards in health centers that possess a realistic, suitable neck and neck of efficacy with comparatively a handful of empty beds at any time.

(iv) Wards in (Zone 4) have low -level BTO and high-level BOR. Such wards have patients with severe, long-lasting diseases or without cause they have long ALS.

This category of investigation has been performed for rapid recognition of badly performing health centers and highlighting areas of direct rectification and discover suitable plans to streamline the incompetence (8). Furthermore, the investigations aim at clear outcomes in the short run period, funding directed at raising health center competence which will be additional advantage in assisting the shift of scare capital to other economical involvements in the same day care situations. Each ward allots themselves particular characteristics by existing in a particular station among the four parts (regions). However, Pabon Lasso has short comings i.e., the performance yardsticks might be strained following a numerous dynamics which cannot be studied by means of a one-dimensional tool (21, 22).

The KCCA is a new administrative body entrusted with management of health service delivery in city whose estimated population is 2.5 million. The authority comprises of five divisions namely: Kampala Central, Nakawa, Lubaga, Makindye and Kawempe with a total of nine health centers and two hospitals. Each division has two health centers apart from Nawaka division. The past few years, emphasis was on quality, quantity, effectiveness & social equity without considerable evaluation of their productivity. This current study performed a Pabon Lasso model to evaluate the condition for the financial year 2012-2013 and discover strategies to assist new management realize high levels of achievement. The purpose of this

study, is to determine the respective performance of the health centers by classifying which zone a health center fits so that the administration team can make additional rational and pertinent judgment of how best to enhance effective performance. More so, to offer administrators evidence they need for appraisal and oversee the health center present activities.

Results

Entirely, nine health centers and two hospitals affiliated to MOH were assessed. The review of collected data showed that the average bed turnover rate, bed occupancy rate and average length of stay were; 74.01, 49.33% and 3.6 days respectively. Table 2 shows the performance yardsticks for the studied wards.

According to Table 2, the highest and lowest BTO rate goes to Intensive Care Ward (284.1) and lowest to Psychiatric Ward (19.3), respectively. In addition, the highest and lowest BOR relate to intensive care ward (98.7%) and female surgical ward (30.6%), respectively. Furthermore, the highest and lowest ALS relate to Psychiatric ward (7.1) and intensive care ward (1.3), respectively.

Real-time analysis of health centers and hospital wards using Pabon Lasso graph showed that from the total of nine health centers and two referral hospitals, Naguru and Mulago, out of the ten wards, Intensive Care and Maternity wards were located in Zone 3, this depicted a High level of efficiency. Two wards of Female Surgical and Postnatal Wards were located in Zone 4, one ward, commonly referred to as other wards, was located in Zone 2. The remaining five wards namely; Pediatric, Male Surgical, Female Surgical, Isolation and Psychiatric were located in Zone 1 Pabon Lasso (figure 1).

Table 2: Performance yardstick of the health centers and hospitals affiliated with ministry of health for the financial year 2012-2013.

	List of wards	No of beds	Admissions	Death	Discharges	In Patient days	Occupancy rate per ward (BOR %)	Bed turnover (BTO)	Average length of stay (ALS)
1	General ward	351	11786	574	12360	66191	51.6	35.2	5.6
2	Paediatric ward	276	11742	439	12181	40122	39.8	44.1	3.4
3	Maternity ward	310	32140	33	32173	69485	61.4	103.6	2.1
4	Male surgical ward	106	3850	69	3919	15364	39.7	37.0	3.9
5	Female surgical ward	73	2949	31	2980	8169	30.6	40.5	2.7
6	Intensive care ward	26	7050	223	7273	9375	98.7	284.1	1.3
7	Postnatal ward	36	2688	1	2689	6157	46.8	75.1	2.2
8	Isolation ward	21	553	8	561	2869	37.4	27.3	5.1
9	Psychiatric ward	3	56	0	56	398	36.3	19.3	7.1
10	Other wards	58	4287	14	4301	10722	50.6	73.6	2.5
	Total	1260	77101	1392	78493	228852	-	-	-
	Average	-	-	-	-	-	49.33	74.01	3.6

Discussion and conclusion

This research used pooled data from eleven MOH health centers and Kampala hospitals. To derive the average performance, we used formulas to calculate BOR, BTO and ALS note indices or mean values. The reason for combined analysis was that data was categorized according to wards and therefore it was mixed. This was to avoid miss reporting or misrepresenting which might result into misleading conclusions. Also another reason was that the type of data and mode collection was in terms of services delivered and by standard. Though the health centers are not similar, one health center is a mirror of the other.

In the past, there was pint-sized investigations of this type in Uganda, and former scholarly works was confined to assessing referral system failures, little investment in the health sector, equitable distribution, comparing public and private not for profit service delivery, abolition of user charges, welfare of health workers, task shifting, unmet health expectations, family planning, quality of life, health infrastructure and HIV/AIDS and its impact. In spite of having many methods for measuring efficiency, MOH has stipulated the average BOR, BTO and ALS following Pabon Lasso. However, health researchers have not ventured in measuring efficiency to help guide policy makers' decisions in the health sector of Uganda.

The graph below indicates the average length of stay, bed turnover and bed occupancy rate as plotted on the graph. The clearly plots each ward for easy analysis of data.

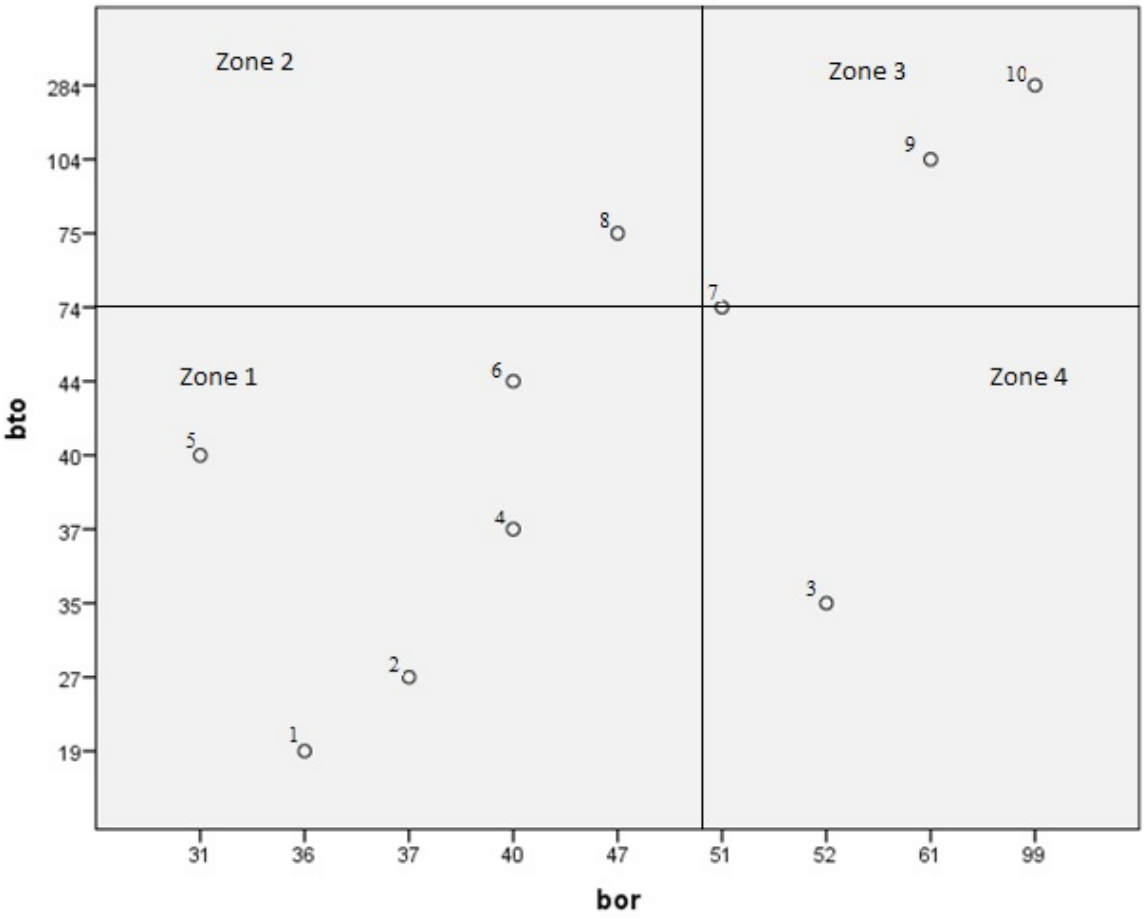

Figure 1: The rank of health centers and hospitals using the Pabon Lasso technique

Care has to be taken while measuring efficiency especially using one yardstick to avoid misleading conclusions on the performance of health centers and hospitals. For instance one can use only BOR and high BOR which may result into either high ALS in some wards due to the nature of illness, cost- effectiveness exhibited in proper management and utilization of resources or simply unnecessary hospitalizations coming from failure to utilize the available resources more efficiently hence leading to inefficiency. Only one study in Uganda used multiple indicators (Pabon Lasson) to measure efficiency of hospitals in Western Uganda in 2002 (7).

This study has used the analytical model for Pabon Lasso which provided us with three yardsticks (BOR, BTO and ALS) as illustrated diagrammatically to support quick evaluation of overall performance and also establish the relationship among the multiple yardsticks to facilitate the analytical and discussion process.

Apart from the fact that data was collected on daily basis and sent to the ministry weekly for a period of one year, it should be noted that certain wards such as, ENT, Eye, TB and Cancer did not exist since TB Ward, is being managed by a Centre for Disease Control.

Overall, the results indicate that only two wards, Intensive Care and Maternity have a good degree of efficiency since they fall in Zone 3 of the Pabon Lasso graph. This means that these two wards may extend to a perfect magnitude of productivity via appropriate service supervision and the observing of the current admissions and delay standards. In Zone 2, we identified one ward that has a low BOR and it appears there are unwarranted hospitalized patients and excess bed capability. Therefore, we propose that appropriate means are engaged to justify the action resourcefully.

General and Postnatal Wards fall into Zone 4 of the Pabon Lasso graph with a low BTO and average BOR but with reduced ALS since any successful delivery does not stay beyond two and half days. Such ALS should be maintained though there is need to improve the BOR and BTO. Among the broad strategies for enhancing performance may include a shift to out-patient for mothers who are not in labour apart from complex cases. There is also need for

comparative studies that will enable comparisons among different hospitals with different status before making any remedial intervention. A number of factors have been identified to be the cause of the state of affairs such as traditional inpatient practices, mismanagement of limited available resources and total failure to utilize the available resources.

The remaining five wards fall into Zone 1, indicating unfortunate accomplishment and ineffective utilization of resources. In the past, many studies have concentrated on performance in terms of absenteeism of health workers (7), immediate intervention is to improve supervision and ensure health workers turn up for duty and work for recommended time. Secondly, health centers should be operational over weekends. This can be managed through shift operations in order to step up the utilization of available resources. Thirdly, full utilization of resources will require improved welfare of health workers more especially in terms staff houses within the vicinity of the health centers (infrastructure). Lastly, there is need for short-term strategies i.e., pause expansion for a while. Focus should be dedicated on identifying factors contributing to the current state of affairs for example inefficiency among the five wards in Kampala health centers and hospital out of ten. Then, immediate interventions like proper resource management, income management strategies, merging nonfunctional wards and departments to reduce on the operational costs and improve on the technology used in terms of equipment should take place (23).

This paper has analyzed 10 wards in Kampala from nine health centers and two referral hospitals under MOH and we assessed their accomplishment through Pabon Lasso model. The end results indicate that although two wards have an outstanding performance, the other eight wards exhibited poor performance. The author has suggested solutions with a view to guide policy makers to improve efficiency.

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PROTEOMICS OF CHONDROGENESIS: A REVIEW

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ABSTRACT

Osteoarthritis (OA) affects millions of people worldwide with its irreversible destruction of articular cartilage. Recently, the potential of using chondrogenic differentiated multipotent mesenchymal stromal cells (cMSCs) for OA treatment is being assessed. Preliminary clinical studies have been encouraging. However current studies have also demonstrated that cMSCs are not biochemically and biomechanically identical to native articular chondrocytes (ACs). Thus, there is an urgent need for the implementation of proteomic applications as proteomics involve protein identification, relative quantification of proteins and studies of post-translational modification which reveal novel regulating processes of complex mechanisms such as in chondrogenesis. A comprehensive understanding of chondrogenesis is essential for the establishment of an effective cMSC model to regenerate cartilage. In this article, we will review current proteomic studies on chondrogenesis, focusing on recent findings and the proteomic approaches utilised.

Keywords: *Chondrocyte, chondrogenesis, proteomic, MSC*

Introduction

Due to the limited intrinsic regenerative capacity of articular cartilage, minor tissue injuries may lead to the development of osteoarthritis (OA), a musculoskeletal disease commonly found in the elderly (1, 2). Recent advances in regenerative medicine have demonstrated that tissue engineering-based constructs enhanced the healing of articular cartilage (3). Using both conventional and sophisticated proteomic approaches, chondrogenic differentiated mesenchymal stromal cell (cMSC) constructs were characterized and conformed to the expression of the chondrogenic phenotype. Several recent studies have shown that although cMSCs expressed the chondrogenic phenotype, a portion of the gene and the protein expression were found deviated from the native articular chondrocytes (ACs) (4, 5). These cells were also biochemically and biomechanically inferior when compared to the native ACs (6-9). Hence, there is a need to develop an effective *in vivo* model to induce and sustain the chondrogenic differentiation of the multipotent mesenchymal stromal cells (MSCs). Before an advance in this area can be achieved, it is essential to have an understanding of the fundamental processes of, and the recent findings in, chondrogenesis. Proteomic aspects of MSC have been described (10 – 12). Thus, this review aims to further update readers on the latest findings of proteomics in chondrogenesis.

Chondrogenesis

Chondrogenesis is a complex process which is directed by a highly regulated consortium of growth factors and signalling molecules. It goes through three stages: an initial condensation of cells which is characterized by N-cadherin; followed by a differentiation characterized by collagen II; and a final terminal differentiation characterized by collagen X (13-15). cMSC expressed a wide range of chondrogenesis related genes including the genes for the SRY (sex determining region Y-box) SOX 5, 6 and 9, type II collagen and aggrecan and secreted a cartilaginous extracellular matrix similar to AC (16, 17). It has demonstrated a potential to replace AC for clinical therapies in the future. In the past, numerous studies focused on the mechanism of chondrogenesis and its signalling pathways (16, 18-20). In the first clinical case where human MSCs were implanted into osteochondral defects, the formation of some cartilage-like tissue was noted (21, 22). However, expanding the micro-scale cartilage formation from *in vitro* to large-scale cartilage tissue engineering still remains a challenge in regenerative medicine.

The advances in technology have allowed more detailed studies to be performed, such as a quantitative evaluation of protein expression at different stages of chondrogenesis, the discovery of new functional proteins involved in the

chondrogenesis pathway as well as the measurement of its cellular mechanical properties (6, 9, 23, 24). These studies demonstrated that cMSC and AC have similar chondrogenic phenotypic expression, but the level of similarity at the molecular aspect remained unresolved (6-9). To illustrate this point, Table 1 summarizes these differences between cMSC and AC in terms of the cellular morphology and the molecular and biomechanical properties.

As listed in *Table 1*, a portion of cMSC genes was expressed differently compared to the AC gene. These differences in gene expression and the morphology and biomechanical properties of cMSC and AC provide evidence that research is needed to determine if these differences are caused by protein expression. Proteins represent the fundamental functional molecules within a cell and they contribute to the mechanical properties of the tissue

Table 1: Evaluation of the molecular, morphological and biomechanical properties between cMSC and AC. (References: 6,7,8,9,23 & 24)

	cMSC	AC
Surface topology	Spherical but flatter with a central hump of condensed mass and a surrounding thin and broad pleat	Spherical
Compressive equilibrium modulus	75-114 kPa Reached plateau at day 28	180-240 kPa Reached plateau at day 42
Dynamic modulus	700-1100 kPa	1000-1400 kPa
Adhesion force	4.54 nN	6.86 nN
Surface stiffness	0.109 N/m	0.134 N/m
Gene expression	324 genes mis-expressed during chondrogenesis of MSC. Under expressed genes: Proteoglycan 4, Similar to MAGEL2 protein, CXCL14, Dickkopf-1, Periostin, ID1, Chondromodulin, TGF-beta induced 68kDa protein (TGFB1), Hox4A, SOSTDC1, Thrombospondin 4, Epithelial V-like Antigen 1, Proteoglycan 4, Similar to Protocadherin 10, Calpain 6, helix-loop-helix transcription factors-HES1, HES5 Over expressed genes: Aggrecan, type II, IX and XI collagen, Similar to leiomodin1, Caspase 4, Meis homeobox 2, Fas, ID1	
Protein expression	No parathyroid hormone-related protein expression	Expressed parathyroid hormone-related protein Higher protein expression: type II collagen, integrin-1,

cMSC chondrogenic differentiated mesenchymal stromal cell; AC articular chondrocyte

(25). Characterization of the cMSC proteome would be informative and worth investigating, as it reflects the actual expression of proteins encoded by a specific gene. In addition, the post-transcriptional regulation processes of protein amount, stability, subcellular localization, post-translational modifications and protein-protein

interactions can only be elucidated at the proteome level (26). Therefore, the importance of proteome analysis of cMSC can never be emphasized enough.

Proteomic Findings on Chondrogenesis

7 significant proteomic related studies on chondrogenesis were identified through a literature search in a ten year period, from 2004 to 2013. The details of these studies are summarized in *Table 2*. Various proteomic approaches were utilised; the advanced non-gel based technique, two –dimensional (2D) online liquid chromatography tandem mass spectrometry (on line LC-MS/MS) and the conventional two –dimensional electrophoresis (2-DE) gel based methods.

The first cMSC proteomic study used a two dimensional electrophoresis coupled with mass spectrometry (2- DE LC MS/MS) to detect the altered proteins due to transforming growth factor b (TGF-b) (27). Human bone marrow derived mesenchymal stromal cells (hbmMSC) cultured in a transforming growth factor (TGF) -b medium led to the identification of 30 altered proteins. The altered proteins consisted of cytoskeleton proteins (16%), cell membrane proteins (9%), ECM proteins (12%), metabolic enzymes (29%), protein synthesis and degradation proteins (9%) and stress response proteins (25%) (27) .

In another study which utilized a similar two-dimensional electrophoresis (2-DE) and mass spectrometry, four chondrogenic differentiated proteins were identified (28). Interestingly, only collagen alpha 1 (II) chain precursor protein was identified in both studies , while the remaining proteins, vascular cell adhesion protein-1 precursor (V-CAM), GTP binding protein RAD and leukaemia inhibitory factor precursor (LIF) cholin were found in the latter study only (28).

In a study using differential gel electrophoresis (DiGE) and umbilical cord stromal derived MSC (ucMSC), De la Fuente *et. al*. identified 39 modulated proteins during chondrogenesis over a forty six day period of the study. With the 2D-DiGE approach 3 protein samples labelled with different fluorescent dyes could be loaded together in one single gel and this allowed for quantitative comparative analyses of all the samples in a single gel with a significant reduction of inter-gel variability. Proteins of the major cell functions of cellular differentiation, proliferation and migration were detected (23). Some of the up-regulated proteins were procollagen-lysine (PLOD2), enolase (ENO1), heat shock protein beta-1 (HSPB1), superoxide dismutase (SOD) and zyxin (ZYX) while down-regulated proteins were calreticulin (CRT), vimentin (VIM) and protein disulfide-isomerase (PDI) (Table 3 and Table 4).

Ji *et. al*. applied a gel free isobaric tag for relative and absolute quantitation (iTRAQ) labeling coupled with 2D LC/MS/MS proteomics technology to quantitate the protein expression profile of an *in vitro* chondrogenic model for six days . In this study, the authors used a murine embryonic mesenchymal cell line, C3H10T1/2. Identified up-regulated proteins were mainly enzymes involved in cartilage extracellular matrix (ECM) synthesis and mature chondrocytes whereas down-regulated proteins were predominantly involved in energy metabolism, chromatin organization, transcription, mRNA processing, signaling transduction and cytoskeleton (Table 3 and Table 4) (24).

Using the technology of stable isotope labelling with amino acids in cell culture (SILAC), Rocha *et. al*. analyzed the cell lysate of a micromass pellet culture at day 2 and day 14 in order to evaluate the protein changes at an advanced differentiation stage (29). hbmMSC were grown in a culture medium supplemented with isotope-labelled amino acids, lysine (Lys) and arginine (Arg). The cells were harvested at designated days and subsequently analyzed with mass spectrometry. Majority of the identified up-regulated proteins were related to cellular metabolism and the glycolytic pathway. Others were involved in protein synthesis and turnover, cytoskeleton organization and chaperones/stress response (Table 3). Some of these proteins were also detected using 2D-DiGE and iTRAQ approach in other chondrogenesis models (23, 24). The reproducibility of the results demonstrated that SILAC could serve as an alternative method for quantitative proteomic studies in the future.

Glycoproteomics

Ishihara *et. al*. utilized a novel glycoform-focused reverse proteomic method to study chondrogenesis (30). Glycoproteomics is a recent proteomic approach which characterizes plasma membrane proteins (31). The investigators performed glycoblotting coupled with high-throughput matrix assisted laser desorption/ionization (MALDI) – time of flight (TOF) mass spectrometry for comprehensive analyses of altered *N*-glycans on ATDC5 cells during chondrogenesis. The identified major components were high-mannose type *N*-glycans which have essential roles in the homeostatic and functional maintenance of the chondrocyte (32, 33). From the 245 identified glycoproteins, five cell surface glycoproteins, collagen alpha-1 (III) chain, collagen alpha-1 (XI) chain, ectonucleotide pyrophosphatase/phosphodiesterase family member 1, aquaporin-1 and netrin receptor (UNC5B) were proposed as candidates for chondrogenic differentiation markers and as pharmaceutical targets in OA (Table 3) (30).

Transplantation Proteomics

After stem cell therapy, proteomic analyses of the tissues and body fluids should be performed to address the safety and feasibility of stem cell therapy. Gong *et. al*. (34) performed an *in vivo* quantitative analysis on the transplanted porcine articular cartilage with native cartilage tissue. This led to the identification of a large number of differentially expressed proteins. Among the identified proteins, 43 proteins in the post – transplantation cartilage tissue exhibited significant quantitative differences from the native tissue (34). These proteins were categorized into four functional groups; glycolysis, cellular organization, signaling pathway and others (Table 3 and Table 4). These

results concurred with previous studies that showed that regenerated cartilage tissue were not identical to native tissue. The identification of these proteins will provide chemical and mechanical clues to improve the quality of engineered cartilage tissues.

Findings of Proteomic Studies

Each of these techniques possesses intrinsic advantages and limitations (35-37). Despite the short-comings, proteomic approaches have revealed many novel cartilage- and OA-related proteins. These identified proteins, are up- or down-regulated during chondrogenesis. These proteins can be categorized according to their proposed functional roles: ECM and cytoskeleton related protein, metabolic enzymes, protein of synthesis and degradation, chaperones and stress related proteins and others and are presented in Tables 3 and 4. (Ref 23, 24, 27, 28, 29, 30, & 34)

Table 2: Summary of the proteomic findings from published chondrogenesis papers

Cell type/ source	Cell Line	Passage/ Culture type	Treatment/ Duration	Proteomic approach	Identified proteins		Differentially expressed proteins	Major result	Ref.
					Total	Unique			
hBM-MSCs	NA	P10, monolayer	10 ng/mL TGF-b1 4 days	2-DE/LC-MS/MS	1500	1	30	The increase of a-actin and the decrease of gelsolin promotes chondrogenesis	(27)
mEMCs	C3H10T1/2	ND, micromass	100 ng/mL hBMP-2 6 days	iTRAQ/2D nanoLC/ MS/ MS	1753	100	100	Biological roles of BTF314 and fibulin-5 were identified and verified involving in chondrogenesis.	(24)
hBM-MSCs	NA	ND, micromass	NA, 2 and 14 days	SILAC/ LC-MALDI-TOF/TOF	622	65	65	Fibronectin, gelsolin, vimentin, alpha-ATPase, mitochondrial superoxide dismutase and cyclophilin A were up-regulated in chondrogenesis.	(29)
rBM-MSCs	NA	P2, monolayer	5 ng/mL TGF-b1, 0, 7, 21 and 28 days	2-DE/ MALDI-TOF-MS	4	4	214 (7-14 day), 37 (14-21 day), 0 (21-28 day)	Vascular cell adhesion protein (V-CAM), GTP binding protein RAD, Collagen alpha 1 (ii) chain precursor and Leukemia inhibitory factor precursor LIF Cholin are identified in chondrogenesis.	28)
hUC-MSCs	NA	P1, spheroid formation	1 ng/mL hTGF-b3, 4, 7, 14, 28 and 46 days	2DE-DIGE/ MALDI-TOF/TOF	54	39	94	15 identified proteins were down-regulated, 21 proteins were up-regulated and 3 proteins were highly modulated during the process.	23)
pASCs	NA	P3, PGA/ PLA scaffold	10 ng/mL TGF-b1, 3 and 6 months	2DE/ MALDI-TOF	43	16	43	The first in vivo proteomic study on chondrogenesis. Alpha-S1-casein precursor, protein disulfide-isomerase A3 precursor, dermcidin precursor and complement factor D precursor with unknown functions were identified.	(34)

Cell type/ source	Cell Line	Passage/ Culture type	Treatment/ Duration	Proteomic approach	Identified proteins		Differentially expressed proteins	Major result	Ref.
					Total	Unique			
mMSCs	ATDC5	P3, pellet	10 ng/mL TGF-b3,	MALDI-TOF-MS	246	5	15	Glycoproteomic study.Levels of high mannose type N-glycans increase during chondrogenic differentiation. Aquaporin-1, collagen alpha-1(III) chain, collagen alpha-1 (XI) chain, ectonucleotide pyrophosphatase/ phosphodiesterase family member 1 and netrin receptor UNC5B are proposed as biomarkers.	30)

Abbreviations: 2D, two-dimentional; 2-DE, two-dimensional gel electrophoresis; pASC, porcine adipose derived stem cell; BM, bone marrow; DIGE, difference in-gel electrophoresis; mEMC, murine embryonic mesenchymal cell; hBM, human bone marrow; iTRAQ. Isobaric tag for relative and absolute quantitation; LC, liquid chromatography; MALDI, matrix-assisted laser desorption/ionization;MS, mass spectrometry; MS/MS, tandem mass spectrometry; MSCs, mesenchymal stem cells; NA, not available; ND, not determined; rBM, rat bone marrow; SILAC, stable isotope labelling by amino acids in cell culture; TGF, transforming growth factor; TOF, time-of-flight; UC, umbilical cord.

Table 3: Identified Up-regulated Proteins Expression during Chondrogenesis.

List of Proteins
ECM and Cytoskeleton related Protein
Annexin A1, A2, A4, A5, A6, Actin-related protein 2/3 complex subunit 4, Actin-related protein 3, Aquaporin-1, Biglycan, Chondroadherin, Collagen alpha-1(III) chain, Collagen alpha-1(XI) chain, Collagen alpha-2(VI) chain, Collagen alpha-3(VI) chain, Ectonucleotide pyrophosphatase/ phosphodiesterase family member 1, Fibronectin, HSP, Netrin receptor UNC5B, Transgelin, Vimentin, Gelsolin, T-plastin, g-Actin, a-Cardiac actin, Collagen-binding protein 2, Tubulin beta chain, Tubulin beta-2C chain, Procollagen-lysine, Zyxin, Transforming growth factor-beta-induced protein ig-h3 precursor
Metabolic Enzymes
Aldose reductase, Alpha-enolase, ATP synthase subunit alpha, ATP synthase subunit beta, Carbonyl reductase, Dihydropyrimidinase-related protein 2, Glyceraldehyde-3-phosphate dehydrogenase, Glycogen phosphorylase, L-Lactate alpha-glucosidase, NADPH dehydrogenase, Nicotinamide N-methyltransferase, Thioredoxin reductase , Malate dehydrogenase, Tyrosyl-tRNA synthetase,UDP-glucose-6-dehydrogenase, Phosphoglycerate kinase 1, Phosphoglycerate mutase 1, Glucose-6-phosphate 1-dehydrogenase, Pyruvate kinase, M2 isozyme, Aldehyde dehydrogenase X, Sodium/potassium-transpoting ATPase subunit alpha-1, Transaldolase, Transketolase, Trisephosphate isomerise, a, b, g-Enolase
Protein Synthesis and Degradation
Aminipeptidase N, Cathepsin B, Cathepsin D, Elongation factor 1-gamma, Histone H2A type 1-C, Histone H4, T-complex protein 1, Ubiquitin carboxyl-terminal hydrolase isozyme L1, Proteasome subunit a type 2, Polymerase I and transcript release factor, Tyrosyl-tRNA synthetase, Heterogeneous nuclear ribonucleoprotein D-like, ADAM Metallopeptidase Domain 15
Chaperones and stress
78 kDa glucose-regulated protein, Endoplasmin, Peroxiredoxin-6, Peptidyl-prolyl cis-trans isomerise A, Superoxide dismutase [Mn], Heat shock protein beta-1, Stress-induced phosphoprotein 1
Others
Caveolin-1, Dolichyl-diphosphooligosac charide–protein glycosyltransferase sub-unit 1, Lactadherin, Heat shock 27-kDa protein, Programmed cell death 6 interacting protein, Septin 6, Peroxiredoxin 2, Chloride intracellular channel protein 4, Nicotinamide N-methyltransferase, Prelamin-A/C, Transforming growth factor-beta-induced protein ig-h3, Transmembrane emp24 domain-containing protein 9, Protein disulfide-isomerase A3

Table 4: Identified Down-regulated Proteins Expression during Chondrogenesis.

List of Proteins
ECM and Cytoskeleton related Protein
Caldesmon, Talin-1, Tropomyosin alpha-4 chain
Metabolic Enzymes
Phosphoglycerate mutase 1
Protein Synthesis and Degradation
Elongation factor 1-delta, Glycyl-tRNA synthetase, Phosphoserine aminotrans-ferase, Poly(rC)-binding protein 1, Serine/ threonine-protein phosphatase PP1-beta catalytic subunit, Reticulocalbin-1,
Chaperones and stress
Heat shock protein beta-1, Peptidyl-prolyl cis-trans isomerase A, Calumenin, Protein SET, Calreticulin, Peroxiredoxin-5, Glutathione S-transferase P, GRP78,
Others
Perilipin-3, Sorting nexin-9, Cysteine and glycine-rich protein 1, SH3 domain-binding glutamic acid-rich-like protein 3, Ferritin light chain, Protein disulfide-isomerase A1, Parathyroid hormone-related protein

Challenges in Proteomic Study and Future Perspective

A major challenge in proteomics is to obtain consistent results across all the studies of chondrogenesis. It remains difficult to draw definitive conclusions from individual studies as each study utilizes a different cell type, passages number, passaging method, chondrogenic differentiation method, and proteomic approach with MS, as the choice and the performance of MS are different in many of the studies. These factors should be taken into careful consideration for the future. Current studies focus only on evaluating the protein changes in the early differentiation process (8). There is no study which directly compares the protein expression and the differences between cMSC and AC. With the growing evidence$_s$ that cMSC is different from AC, more studies should be conducted to determine the cause of these differences.

Concluding Remarks

Proteomic approaches can generate large data sets of the proteins involved in the mechanisms and pathways of chondrogenesis. These studies will lead to a better understanding of chondrogenesis and the processes of its differentiation. Current reviews of research data are relatively preliminary, but the outcome data is still very interesting. Robust and rigorous studies in the future would allow for more definitive conclusions. In the near future, with the improvement in chemical-labelling reagents and MS performance, large-scale MS-based protein quantification approaches will become more economically possible and will significantly improve research on chondrogenesis that can lead to better outcome findings.

Disclosure of Potential Conflicts of Interest

The author indicates no potential conflicts of interest.

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