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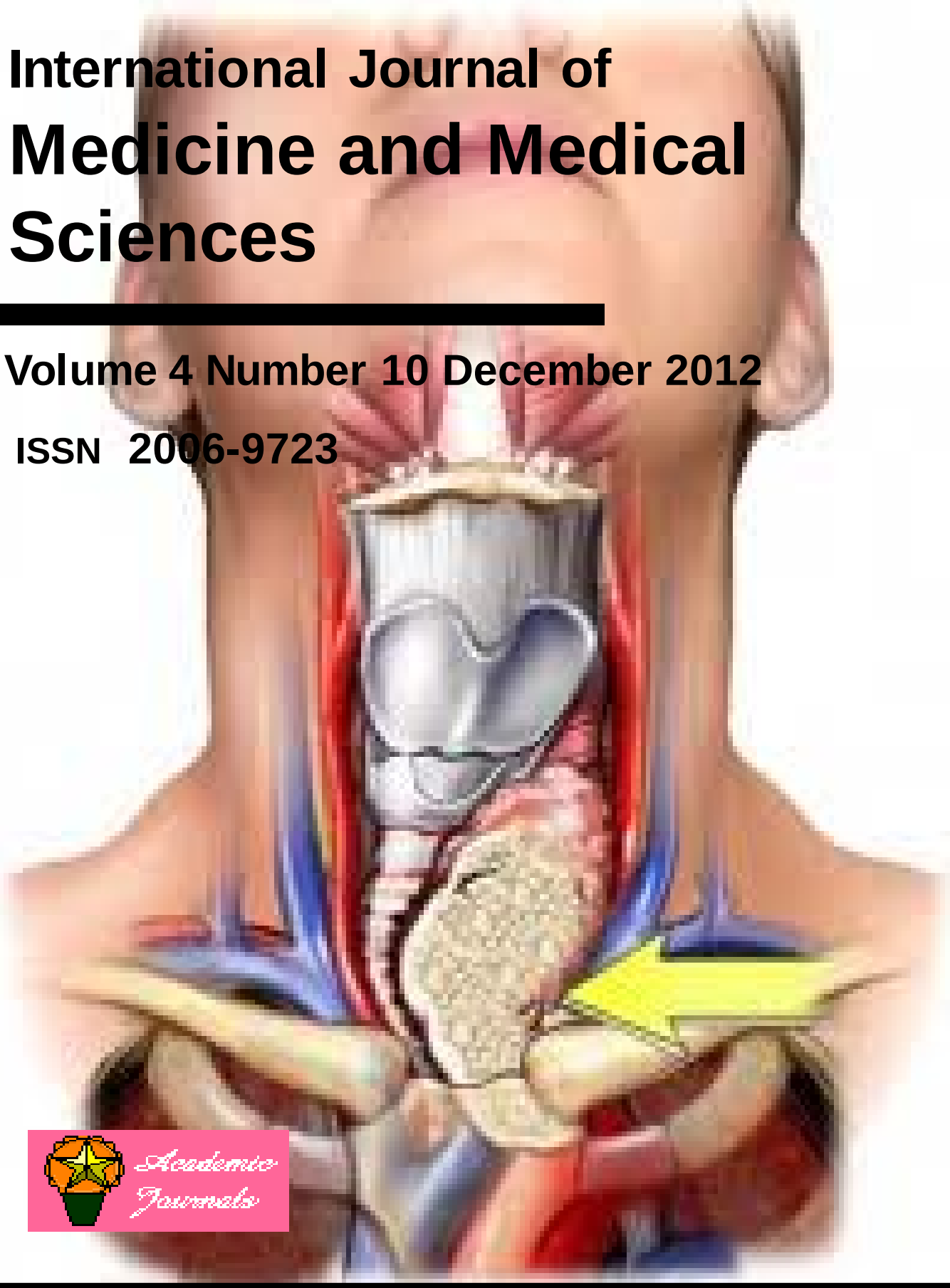

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Mussel RL, De Sa Silva E, Costa AM, Mandarim-De-Lacerda CA (2003). Mast cells in tissue response to dentistry materials: an adhesive resin, a calcium hydroxide and a glass ionomer cement. J. Cell. Mol. Med. 7:171-178.

Booth M, Bundy DA, Albonico P, Chwaya M, Alawi K (1998). Associations among multiple geohelminth infections in school children from Pemba Island. Parasitol. 116: 85-93.0.

Fransiscus RG, Long JC, (1991). Variation in human nasal height and breath, Am. J. Phys. Anthropol. 85(4):419-427.

Stanislawski L, Lefeuvre M, Bourd K, Soheili-Majd E, Goldberg M, Perianin A (2003). TEGDMA-induced toxicity in human fibroblasts is associated with early and drastic glutathione depletion with subsequent production of oxygen reactive species. J. Biomed. Res. 66:476-82.

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Case Report

Tracheobronchopatia osteochondroplastica: An underdiagnosed central airway disease

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Accepted 6 November, 2012

In the population of patients who do not smoke, do not take an angiotensin-converting-enzyme inhibitor, and have a normal chest radiograph, upper airway cough syndrome, asthma, gastroesophageal reflux disease and chronic bronchitis are responsible for approximately 99% of cases of chronic cough. The diagnosis is often based upon the patient's response to empiric therapy; nevertheless, there still remains 1% with an undiagnosed etiology. We report a case of a 76 year old female who had presented with persistent cough for roughly four decades requiring hospitalizations on multiple occasions. Despite receiving empiric therapy and the standard of care management for bronchial asthma, her symptoms were progressively getting worse. Physical examination and laboratory workup were unremarkable. Pulmonary function test was abnormal; the flow volume loop demonstrated a flattening of the inspiratory phase, which resulted into why an extrathoracic obstruction was suggested to require further workup. A chest computed tomography revealed a proliferation of bone and cartilage in the anterior and lateral walls of the trachea sparing the posterior wall. Multiple submucosal sessile cartilaginous nodules were detected by flexible bronchospy. Tissue sampling resulted in a mucosal squamous metaplasia, all findings consistent with tracheobronchopatia osteochondroplastica. The patient was treated with laser therapy with physiological and clinical response.

Key words: Tracheobronchopatia osteochondroplastica, extrathoracic obstruction, osteocartilaginous nodules, central airway obstruction, chronic cough.

INTRODUCTION

Tracheobronchopathia osteochondroplastica is an idiopathic rare disease of the trachea and major bronchi characterized by multiple submucosal osteocartilaginous nodules that protrude into the lumen sparing the posterior wall. The first case was described in 1857 as "Ossific deposits on the larynx, trachea and bronchi" found incidentally in a patient at an autopsy (Abu-Hijleh et al., 2008; Leske et al., 2001). Cases reported in 1863 were termed as "ecchondrosis and exostosis" (Leske et al., 2001). It was not until 1910 when the entity was named "tracheobronchopathia osteochondroplastica" due to its clinical presentation (Leske et al., 2001).

TBO is an unknown entity seen with a frequency of 0.4% at bronchoscopy (Chroneou et al., 2008). There is no gender predominance and the disease typically manifest in patients in their mid-50s. The clinical presentation is variable, ranging from incidental diagnosis in asymptomatic patients to devastating disease, causing central airway obstruction (Tukiainen et al., 1998). Due to recent advances in modern technology, the disease has been well recognized early in its course and prompt treatment implemented.

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Abbreviations: **TBO,** Tracheobronchopatia osteochondroplastica; **PFT,** pulmonary function test; **FEV1,** forced expiratory volume in one second; **FVC,** forced vital capacity.

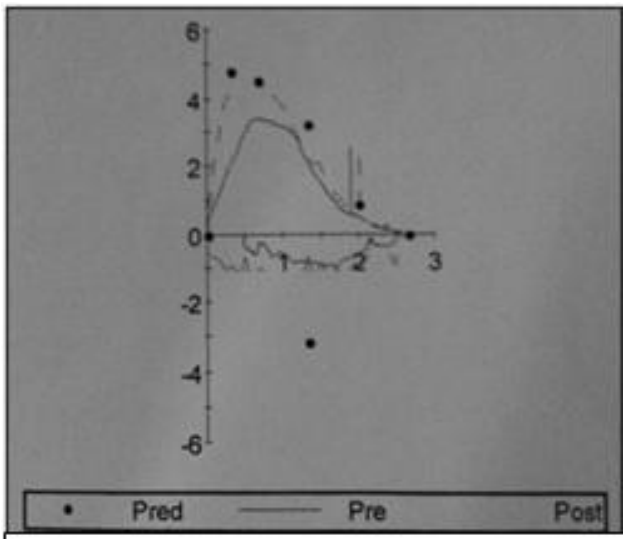

Figure 1. Flow volume loop demonstrating flattening of the inspiratory phase.

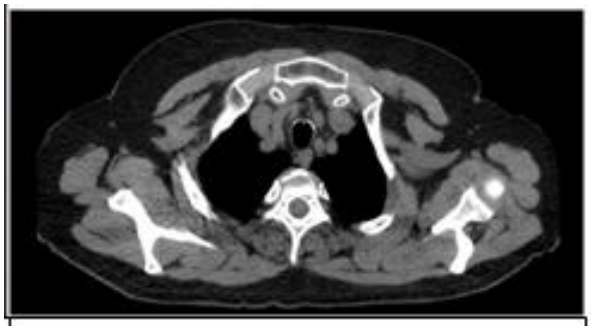

Figure 2. Chest tomography with poliferation of bone and cartilage in the anterior trachea

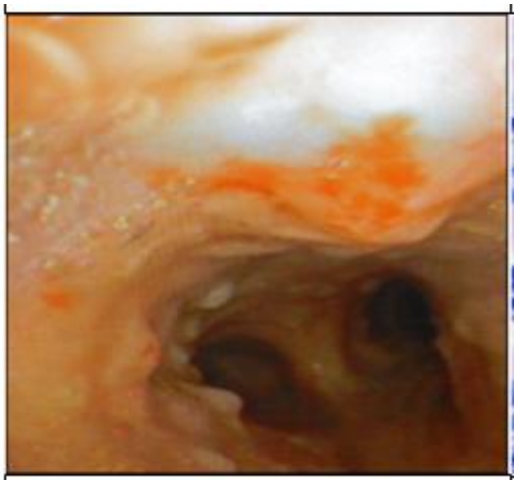

Figure 3. Bronchoscopy displaying multiple submucosal sessile cartilaginous nodules.

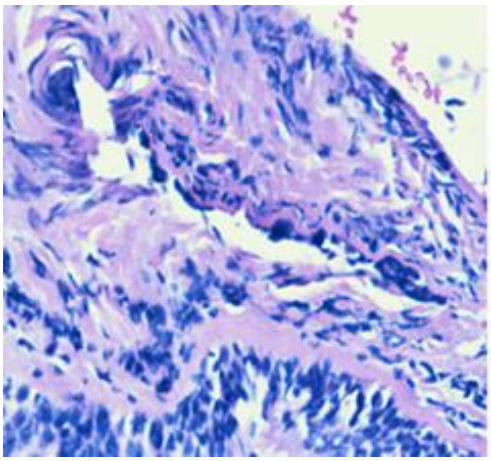

Figure 4. Giesma stain exhibiting mucosal squamous metaplasia.

CASE REPORT

We present a case of a 76 year-old female, non-smoker, with a past medical history of arterial hypertension, hypothyroidism, dyslipidemia and bladder cancer with tumor resection at the age of 35. Neither chemotherapy nor radiotherapy was necessary for the above condition at the time of diagnosis and no occupational or environmental exposures to fumes or dust was pertinent in the history. The patient sought medical attention after complaining of persistent nonproductive cough for the last forty years requiring hospitalizations on several occasions. Within this period, she always had been treated with the usual management for bronchial asthma since her clinical manifestations were misdiagnosed with this obstructive and chronic disease.

Despite receiving the standard of care management for bronchial asthma, her symptoms had been worsening over the past few years. At age 73, as part of the initial evaluation, the physical examination and laboratory workup were unremarkable including complete blood count, complete metabolic panel and thyroid function. No abnormal findings on chest auscultation such as inspiratory/expiratory rhonchi, wheezing, stridor, nor crackles were detected. PFT was significant for FEV_1 1.93 L (94% predicted value) and FEV_1/FVC 76% (101% predicted value), nevertheless the flow volume loop was remarkable for flattening of the inspiratory phase (Figure 1), reason why an extrathoracic obstruction was suggested leading to further studies. These included a chest computed tomography (Figure 2) which revealed a proliferation of bone and cartilage in the anterior and lateral walls of the trachea just to the level of the carina and proximal half of bilateral main bronchi sparing the posterior wall suggestive of TBO. In order to have a definite diagnosis of the condition, a bronchoscopy (Figure 3) was performed which was remarkable for multiple submucosal sessile cartilaginous nodules. The biopsy (Figure 4) demonstrated mucosal squamous metaplasia, commonly seen in TBO. The patient was treated with laser therapy with physiological and clinical response. Further, PFT demonstrated an improvement of the previously seen obstructive impairment and flattening of the inspiratory phase.

DISCUSSION

The etiology remains uncertain, though several theories

about the pathogenesis have been linked to bone morphogenetic protein-2 (BMP-2) and transforming growth factor β1 (TGF-β1) (Prince et al., 2002). Due to the indistinct symptomatology which chronic cough appears to be the most common clinical presentation, the disease can go unnoticed and misdiagnosed. Nevertheless, with advances in techniques including the development of bronchoscopy and airway images, the detection has been increasing although still the overall incidence remains low. Treatment is reserve for symptomatic patients. It is palliative and it includes local laser, mechanical debulking using a rigid bronchoscope, and endobronchial stent placement. The outcomes are variable. An untreated condition can lead to a devastating outcome due to worsening of the obstructive disease for which clinicians should consider as a differential diagnosis. Hence, primary care physicians should be aware that obstructive patterns in the PFTs not only are secondary to conditions such as Chronic obstructive pulmonary disease (COPD) or bronchial asthma.

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Full Length Research Paper

Adoption of criteria of blood donors selection for blood screening in hospitals of Islamabad

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The study was conducted with the objective to determine the adoption of criteria of blood donor selection for blood screening in hospitals of Islamabad, Pakistan. The criteria of blood donor selection were supposed to be based on World Health Organization (WHO) standards and National Health care guidelines. It was observed that blood donors were mostly the relatives of patients. The age, weight, physical condition, temperature, history of addiction and alcohol effect at time of blood donation was in accordance with WHO blood donation criteria. However, pulse, hemoglobin, respiratory diseases and skin diseases were not determined in all the blood banks of hospitals in Islamabad and were in clear violation of WHO standards and National Health care guidelines, indicating that only few WHO standards and national healthcare guidelines were followed, but majority of them were missing or not followed appropriately. The study revealed that the criteria of blood donor selection were not fully followed in hospitals of Islamabad, and this needs to be rectified. Moreover, blood donors should be motivated to donate blood on voluntary basis. Similarly, the study may be conducted in other part of Pakistan as well.

Key words: Blood donor selection, World Health Organisation (WHO) standards, hospitals, Islamabad.

INTRODUCTION

World Health Organization (2009) narrated that safe blood transfusion is basic human right, and provision of safe blood and blood component is a responsibility of National health care system. In the world, 230 million operations are carried out annually that require substantial quantity of safe blood for transfusion. In Pakistan, situation pertaining to safe blood transfusion is quite unsatisfactory as documented by Zaheer (2009). This is due to fragmented, rampant commercialized and poor quality, unorganized transfusion services that prevail in most parts of the country. The blood transfusion services are mostly hospital based, with 170 public and 450 private blood banks. There were no separate independent blood banks, but usually one or two rooms in a hospital were allocated and designed as blood bank. The blood bank falls under the administrative and financial control of a hospital in which it is located.

In Pakistan, 1.5 million bags of blood are transfused annually, with only 40% blood demand being met by public sector and the remaining 60% by private sector blood banks. At present, the shortage of blood approximates to 40%. The safe blood transfusion is an integral part of modern health care system, as patients of Thalesemia, Haemophelia, Dialysis and Hepatitis need regular and constant blood transfusion throughout their whole life. This necessitates that blood donation may be a regular feature to cope with the requirement of patients outlined above.

The safe blood transfusion is a function of many variables, the most important one being the criteria of blood donor selection. The human blood is a valuable resource of immense significance, the cost of which may not be assessed on monetary basis. According to World Health Organization survey report, in developed countries, 100% blood is donated on voluntary basis (Jang, 2011) while in Pakistan, the situation pertaining to blood donation is not only quite different but contrasting, as well, as 70% blood donation by relatives, 20% by professional blood donors and only 10% on voluntary basis. This may be attributed to lack of awareness among

masses, no screening facility for general public and non existence of regular blood bank. The blood donated by professional is fatal for transfusion to patients, as it is a nursery rather rich source of hepatitis and other blood related diseases.

Some of the professional blood donors are addicted persons that use heroin and other necrotic drugs. Shamsi (1995) in Karachi conducted blood screening study of 135 professional blood donors and showed that 11% were subjected to hepatitis B virus (HBV) and 21% were suffering from hepatitis C virus (HCV). This indicated that every third person was responsible for the spread of HBV and HCV in the society. Hepatitis is spreading at an alarming rate in Pakistan.

Pakistan Medical Research Council (2009) inferred from investigations that prevalence of HBV and HCV in general population of country was 11.84 million during 2007 to 2008. According to WHO (2009) standards, for safe blood acquisition, donor age for both male and female must be 18 to 60 years, weight not less than 45 kg. The donor may be in sound health, free from any diseases not accustomed to permanent medication, not subjected to malaria attack during previous year and had not received blood at any time. The donor may not be a patient of infectious and blood related diseases. The syringe of blood collection may be disposable and incinerated after use.

According to Shamsi (2011), nature had inbuilt storage system of blood in human body equivalent to three excessive bottles over and above that of body requirements. This excessive blood is available for donation periodically without hampering the normal function of body. However, only one bottle may be taken, other excessive blood may cope with body need in case of road accidents that are common in Pakistan and other bleeding from the body. In case of excessive bleeding, blood transfusion from external source is vital otherwise, death may occur because of scarcity of blood. Many deaths in Pakistan only occur because of scarcity of blood.

A healthy person may donate one bag of blood after every three months, four times as year and a healthy woman may donate blood twice a year. The blood donation is a healthy phenomenon, as it controls cholesterol, fatness and inculcate disease resistance in human body. The quantity of old blood is replaced with equivalent, new, fresh, safe, healthy blood in a short span of time that impart new vigor to human body. WHO (2009) emphasized that to avoid collection of unsafe blood, the preliminary test may be performed before taking blood for screening, otherwise it may tantamount to wastage of resources.

If blood is proclaimed safe, then more blood may be taken in bag and stored at optimum temperature and conducive environments. In the well managed hospitals, life of three patients can be saved from a single bag of blood. This is important that blood may not be taken from donors that do not fulfill the WHO blood donor criteria and are subject to HBV, HCV and human immunodeficiency virus (HIV) and other infectious diseases. The blood may also not be taken from addiction, narcotic use, specifically heroin addiction persons. They must not have taken alcohol at time of blood donation (Rehman, 2011; Gerizy, 2009; Hassan, 2011).

In donor selection, it may be kept in view that technicians had adequate knowledge of period of deferment in case of typhoid fever, malaria, hepatitis vaccination and breast feeding. The technicians may also be aware of permanent deferment in case of cancer, heart disease, gammagloubin, weight loss, diabetes, Asthma, Tuberculosis, Epilepsy, Leprosy, Schizophrenia and endocrine diseases.

The transfusion of safe blood is vital to avoid spread of infectious diseases and ensure healthy life. The preceding discussion necessitated that voluntarily blood donors in Pakistan are to be motivated and to achieve this objective; the blood screening facility may be available to general public, which at present is only available to patients. Furthermore, proper counseling of donor may be taken up by blood banks. In order to determine whether WHO criteria of donor blood selection are followed, a study was conducted with the objective to assess the adoption of criteria of blood donor selection in hospital of Islamabad.

MATERIALS AND METHODS

The study was conducted in Islamabad capital territory. The hospitals were selected by simple random method and out of 5 hospitals, 3 hospitals were selected at random. The three main hospitals were selected where more than 70% of the total patients visit. In the capital city, somehow the practices are better as compared to the rest of the country but still not according to the WHO standards. Hence, the current study was carried out to estimate the practices adopted for the selection of the blood donors. The blood bank of one or two rooms was located in the respective hospital. The blood facility in three blood banks was coded as blood bank facility I (BBF1), BBF2 and BBF3, respectively. This was done to accrue confidentiality of blood banks under study. The study design adopted was descriptive and cross sectional. The data collected was based on structured questionnaire. All concerned were informed about objective of the study.

The data pertaining to donor selection involve age, body weights, physical condition, interval between blood collection, temperature, pulse, hemoglobin value, respiratory disease, jail mate, history of drug addiction, alcohol effect at time of donation, consciousness, hepatitis vaccination, malaria incidence, typhoid fever, heart attack and other diseases. In BBF1, whole blood, and in BBF2 and BBF3, small portion for screening was collected. In BBF1 and BBF3, 450 ml blood was collected, while in BBF2, 500 ml blood was collected. First in First out (FIFO) policy was adopted in all three blood banks. The blood units donated during six months in three hospitals of Islamabad were 13,133, of which in BBF1, 2,616, in BBF2, 10,119 and in BBF3, 398 blood bags were donated.

The data collected was entered in Special Package for Social Sciences-17 (SPSS-17) for analysis. The results were tabulated

Table 1. Criteria of blood donor's selection for blood screening in Hospitals of Islamabad.

S/N	Criterion of blood donors selection	Blood bank facility		
		BBF1	**BBF2**	**BBF3**
1	Initial quantity	Whole blood was collected prior to screening	Small portion was collected prior to screening	Small portion was collected prior to screening
2	Physician examination of donor was conducted	Yes	Yes	Yes
3	Interval between blood collection	Three months	Three months	Three months
4	Quantity of blood collected	450	500	450
5	Age of blood donor (years)	18-60	18-60	18-60
6	Weight not less than (kg)	45	45	45
7	Temperature of donor	Checked	Checked	Checked
8	Pulse, hemoglobin, respiratory disease, skin disease	Not checked	Not checked	Not checked
9	History of addiction, alcohol effect at time of blood donation	Checked	Checked	Checked
10	Deferment period in rabies vaccination	Known	Not Known	Not Known
11	Deferment period in cholera, typhoid, tetanus, plague and gammagloubin	Not Known	Not Known	Not Known
12	Deferment period in hepatitis vaccination	Known	Known	Known
13	Deferment in cancer, heart diseases, diabetes, weight loss, TB, liver diseases-permanent	Known	Known	Known
14	Deferment in asthma, epilepsy, leprosy-permanent	Known	Known	Known

BBF1 - Blood bank facility 1, BBF2 - blood bank facility 2, BBF3 - blood bank facility 3.

and presented as frequency/percentage. Based on data, inferences were drawn accordingly. It was ascertained whether WHO or National health care guidelines pertaining to blood donor selection were followed or otherwise, in hospitals of Islamabad. Conclusions were drawn and suggestions for future research made.

RESULTS AND DISCUSSION

The data pertaining to criteria of blood selection for blood screening in hospitals of Islamabad is presented in Table 1 and frequency is given in Table 2. In all three blood banks of three hospitals of Islamabad, the total number of blood bag screened during six months were 13,133, out of which 2,616, 10, 119 and 398 blood bags were that of blood bank facility 1, blood bank facility 2 and blood bank facility 3, respectively. All the blood donated in Islamabad capital territory was that of the relatives.

Figure 1 indicates the quantity of blood collected in the hospitals of Islamabad. The Quantity in different hospitals vary from 440-500.

Figure 2 indicates the deferment period in hepatitis vaccination known. In majority of the hospitals the respondents have idea about the deferment period. Contrary in case of rabies hepatitis vaccination few of the hospitals have idea regarding deferment period as indicated in Figure 3. The Figure 4 indicates the information regarding initial quantity and majority of the hospitals have information regarding initial quantity.

The World Health Organization (2011) conducted a survey pertaining to blood donation and reported that in developed countries, almost 100% blood is donated voluntarily, while in Pakistan, 70% blood is donated by relatives, 20% by professional blood donors and 10% is donated on voluntarily basis. This is an alarming situation and calls for the attention of national health care system. The awareness of voluntarily blood donation may be propagated earnestly. Furthermore, the blood donated by relatives is mostly transfused to relative patients that may cause Acute graft versus host disease (A-GVHD) that is fatal and may result in mortality of up to 90%. Because of lack of know-ledge, relatives also emphasizes that the blood donated by them should be transfused

Table 2. Criteria of blood donors selection for blood screening in Hospitals of Islamabad.

S/No.	Criteria of blood donors selection	Frequency (%)			
		BBF1	BBF2	BBF3	Average
1	Physical of examination of blood donor	100	100	100	100
2	Interval of three months between blood collection	100	100	100	100
3	Age of blood donor (18-60 years)	100	100	100	100
4	Weight not <45 kg	100	100	100	100
5	Temperature checked	100	100	100	100
6	Pulse, hemoglobin, skin and respiratory diseases checked	0	0	0	0
7	History of addiction, alcohol effect checked	100	100	100	100
8	Deferment period in rabies vaccination-known	100	0	0	33.3
9	Deferment period in cholera, typhoid, tetanus, plague and gammagloubin-Known	0	0	0	0
10	Deferment period in hepatitis vaccination-Known	100	100	0	66.7
11	Deferment in cancer, heart disease and diabetes-known	100	100	100	100
12	Deferment in weight loss-TB and liver disease-known	100	100	100	100
13	Deferment in asthma, epilepsy and leprosy-known	100	100	100	100
14	Initial quantity of blood taken-small	0	100	100	66.7

BBF1 - Blood bank facility 1, BBF2 - blood bank facility 2, BBF3 - blood bank facility 3.

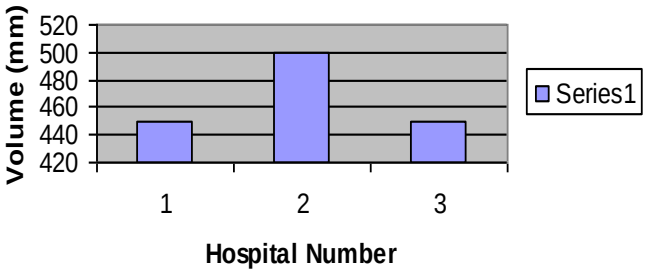

Figure 1. Quantity of blood collected in hospitals of Islamabad.

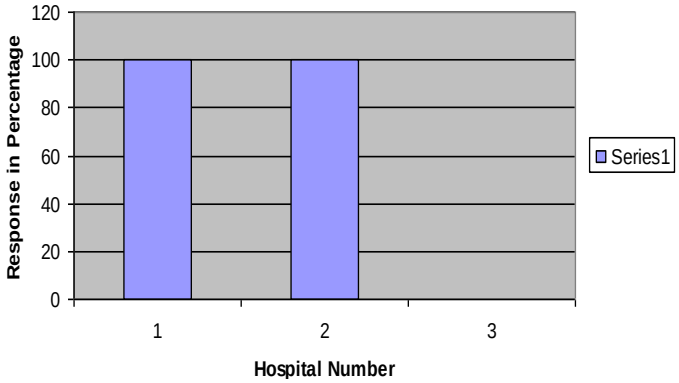

Figure 2. Deferment period in hepatitis vaccination-known.

to their relatives only.

Shamsi (2011) advocated that to avoid A-GVHD, blood donated by relatives may be replaced with blood of other donor persons. The most crucial state of affair is that in

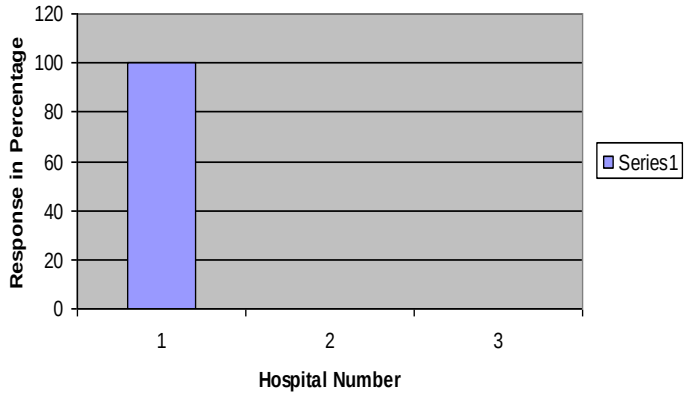

Figure 3. Deferment period in rabies hepatitis vaccination-known.

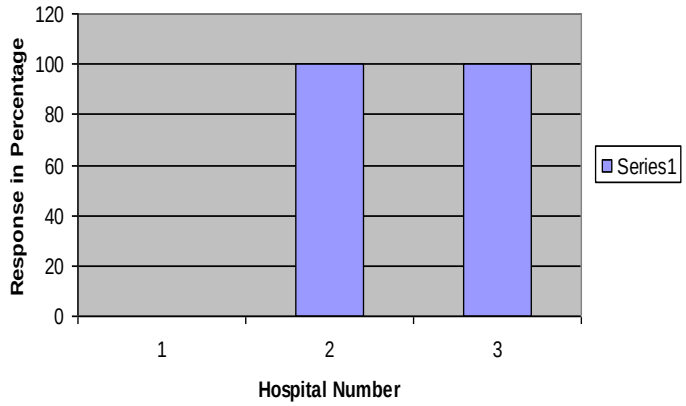

Figure 4. Initial quantity of blood taken was small.

Pakistan, substantial quantity of blood, 20%, is donated by professional blood donors; those subjected to addiction and narcotic use, mostly to heroin addiction. This group of blood donors act as carrier of HBV, HCV and other blood related diseases and transmit to persons to whom such blood is transfused. The group for safe blood transfusion is that of voluntary donors that constitute only 10% of blood donors in Pakistan. In advanced countries, the blood donation is a regular feature and scarcity of blood is a distant problem, while in Pakistan, scarcity of blood is 40% for many patients, specifically road accidents because of excessive bleeding, as no blood is available for transfusion. The public in Pakistan needs to be motivated to donate blood voluntary, and also screening facility may be available to common man, as at present, it is only available to the patients, as was observed in present study in hospitals of Islamabad. The notion prevalent among masses may be shed-forth with the fact that blood donation weakens the health, rather it may be advocated that blood donation inculcate healthy life and more vigour by replacement of old blood with new blood. This also controls cholesterol, fatness and induce resistant to diseases. The blood replacement occurs instantaneously as it is a log and not a lag phenomenon.

As regards to criteria of blood donors, the data in Tables 1 and 2 revealed that age of old blood donors was between 18 to 60 years and weight of donors was not less than 45 kg, and this was determined prior to blood donation. The physical examination of blood donors in all three blood banks was conducted and donors have good physique. The temperature of donors was also recorded. The history of addiction was determined, alcohol effect at time of blood donation was also checked and donors were free from these menaces when blood was taken for donation. All these observations were in line with WHO blood donor criteria and also prerequisite of blood donation according to national health care policy. Contrary to this and in violation of WHO standards, pulse, haemoglobin, respiratory diseases and skin diseases were not checked in all three blood banks of hospitals of Islamabad. The interval between blood collection was three months in all the hospitals under investigation. As such, a healthy person may donate blood four times a year. However, a woman according to Shamsi (2011) investigations may donate blood only two times a year. This is in coincidence to WHO (2009) criteria that interval between two blood donation by a healthy person may not be less than three months.

BBF1 whole blood, 450 ml, was taken prior to screening, which was clear contradiction of WHO guidelines which narrated that small portion of blood may be taken prior to screening, otherwise, if confirmed positive, it may result in wastage of time, labour and resources. However, in BBF2 and BBF3, the guidelines of WHO were kept in view, and small portion of blood was collected prior to screening. After screening, blood collected in BBF2 was 500 ml and in BBF3 was 450 ml. The blood was stored in plastic bags as prescribed by Walter (1948), prior to that, that blood was stored in glass bottles. The plastic bags are easy to handle and transfuse blood to patient. The deferment period in rabies vaccination was known in BFF1 and was not known in BBF2 and BBF3. However, deferment period in cholera, typhoid, tetanus, plaque and gammgloubin was not known in all three blood banks. As regards deferment period in case of hepatitis vaccination, it was known in BBF1 and BBF2 and not known in BBF3. The technician in all three hospitals of Islamabad had knowledge of permanent deferment in case of cancer, heart disease, diabetes, weight loss, liver disease, asthma, epilepsy and leprosy.

It is worthwhile that facility for screening of HBV, HCV and HIV was available in three blood banks of Islamabad. The number of HBV positive donation in six months was 251 out of a total of 13,133 blood donations. The number of HBV positive donation was 82, 163 and 6 in BBF1, BBF2 and BBF3, respectively. The number of HCV positive donations in six months was 236, 306 and 34 in BBF1, BBF2 and BBF3, respectively, and this constituted a total of 576 HCV positive donations. The number of HIV positive donation was only 4 out of 13,133. This revealed that HCV was more prevalent than other viruses and was quite fatal for human life in Pakistan. The occurrence of HIV, though nominal, still is a great alarm and may pose a severe threat to human health in the country in future. This is commendable that in hospitals of Islamabad, positive donations are kept separately and no such transfusion with such blood donations is in practice. However, it poses a valid question. “Is this practice carried out all over the country?

Blood transfusion authorities are to be made effective to streamline the network of blood banks in order to follow the WHO standards and national health care guidelines, specifically in criteria of blood donor selection, so that safe blood is available for transfusion to save human life. Moreover, voluntary blood donation may be encouraged and on national day every healthy person may donate one bag of blood voluntarily.

CONCLUSION AND RECOMMENDATION

Criteria of blood donor selection for blood screening in hospitals of Islamabad are not followed as prescribed by WHO standards or National health care guidelines. The criteria of blood donor selection may be ensured in hospitals of Islamabad and also elsewhere in other part of Pakistan so that safe blood is available for transfusion to patients. The voluntary blood donation may be propagated so as to curtail deaths due to scarcity of blood that occur frequently in Pakistan. Similar study may

be extended to rural area of country and awareness pertaining to voluntary blood donation may be imparted to the general public in remote areas of the country as well.

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Full Length Research paper

Genetic susceptibility for type 2 diabetes mellitus among North American Aboriginals

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Type 2 diabetes (T2D) is a complex human disease which has become extremely prevalent among indigenous populations of Canada and the United States in recent decades. T2D is etiologically complex and refers to a group of disparate metabolic diseases, having major genetic and environmental risk factors. It is believed that a combination of genetic susceptibility and lifestyle changes among indigenous people are to blame for the recent diabetes epidemic. Hypotheses for possible thrifty genotypes and phenotypes have been proposed to explain the causes of the high incidence of T2D in North American Aboriginal populations. Non-genetic factors such as income, living conditions and crime rates also show evidence of affecting T2D risk among Aboriginal people through physiological stress mechanisms. Recent advances in genetic technology have facilitated the identification of a number of gene variants that show positive predictive and diagnostic value for T2D. One of these genes is specific to a group of Aboriginal people in Canada and its occurrence is consistent with the thrifty genotype hypothesis. Identification of susceptibility genes can provide researchers with a starting point for understanding the specific metabolic processes responsible for causing T2D in different populations. This information can be used for producing methods of therapeutic intervention in the future. In the meantime, reducing environmental risk factors for T2D through lifestyle changes remain an important means of preventing the expression of the disease phenotype in Native American and Canadian Aboriginal people.

Key words: Type 2 diabetes, Aboriginals, North America, genetic and non-genetic factors.

INTRODUCTION

Clinical description of diabetes

Diabetes is not a simple disease. It has numerous causes and manifestations, all with the common feature of chronic elevated plasma glucose levels (ADAM Medical Encyclopedia, 2011). Four categories of diabetes have been classified by the United States National Diabetes Data Group and were later accepted by the World Health Organization (WHO). They include type 1 or insulin dependent diabetes mellitus (T1D), type 2 or non-insulin dependent diabetes mellitus (T2D), gestational diabetes (GDM), and diabetes associated with rare inherited syndromes and other disease states (ADAM Medical Encyclopedia, 2011; Szathmáry, 1994). Among these forms of diabetes, T2D is exceedingly the most common, with recent estimates showing that more than 90% of the over 18 million North Americans with diabetes have T2D (Center for Disease Control and Prevention, 1997; Inzucchi and Sherwin, 2005).

Like other forms of diabetes, T2D and T1D are typically caused by a disruption in one of a number of molecular signalling pathways involved in glucose metabolism. The major metabolic defects characterising T2D are resistance of the liver, muscle and peripheral tissues to circulating insulin for glucose uptake, and β-cell insensitivity to glucose for insulin production (Szathmáry, 1994; Surwit and Schneider, 1993).

Insulin is a hormone produced by the pancreas in response to stimuli such as the absorption of ingested glucose or protein into the blood (Szathmáry, 1994). Insulin regulates carbohydrate metabolism by signalling liver and muscle tissues to take up glucose from circulating

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blood and store it as glycogen. Insulin also suppresses the release of glucagon, thus inhibiting the use of fat as an energy source (Szathmáry, 1994). For some patients with T2D, insulin secretion is greater than normal and for others it is compromised (similar to T1D). For those who experience insufficient insulin secretion from the pancreas in response to glucose stimulation, peripheral tissue insulin resistance may only be minimal (Banerji and Lebovitz, 1989). With T1D, insulin is produced by the β-cells of the pancreas at below normal rates or not at all. This reduction in insulin secretion is induced by an auto-immune process, where the body's immune system targets and destroys the insulin-producing β-cells of the pancreatic Islets of Langerhans (Surwit and Schneider, 1993; Altmüller et al., 2001).

The different forms of diabetes have similar long-term complications which are related to the damage of organs and blood vessels from chronic hyperglycaemia, as the liver over secretes glucose into the blood because of disrupted insulin signalling (Szathmáry, 1994). These complications include cardiovascular disease, end-stage renal disease, retinopathy, leading to blindness and gangrene of the extremities (Wetterhall et al., 1992; Young et al., 2000). Additionally, glucose toxicity may eventually destroy the insulin secretory capability of the pancreas and contribute to insulin resistance in other tissues, further impairing glucose metabolism (Kajimoto and Kawamori, 2002; Leahy, 1990; Diabetes and Geneics Initiative, 2007). Because diabetes is a chronic disease, the rate and severity of complications generally rises as the age of onset decreases (Lillioja and Wilton, 2009). Living with these complications means that many patients suffering from diabetes will experience pre-mature death or disability as well as a compromised quality of life (Young et al., 2000).

Genetic complexity

The multifactorial nature of diabetes is a major cause of its scientific complexity. Many different genes must function correctly for all of the cellular signalling pathways involved in glucose metabolism to work properly. Therefore, diabetes may be defined by a number of subtly different phenotypes, all created by various genetic abnormalities (Lillioja and Wilton, 2009; Busch and Hegele, 2002). T2D, which is often viewed as a single disease, is actually caused by a number of distinct meta-bolic defects which all result in similar symptomatic features.

Many characteristics of T2D make it a difficult disease to understand genetically. First of all, it is phenotypically complex. There are different clinical forms of diabetes with varying ages of onset, insulin secretion and insulin resistance. Insulin resistance is also something which can be caused independently by environmental agents (diet) or by one or more genetic mutations (phenocopies) (Altmüller et al., 2001; Hattersley et al., 2009; Haman et al., 2010).

Gene-environment interaction adds to the etiologic complexity by reducing the experimental association be-tween the disease phenotype and susceptibility genes (Hauser and Boehnke, 1998; Weeks and Lathrop, 1995). Additionally, genes may have incomplete penetrance, meaning that individuals who are genetically predisposed may fail to express the disease phenotype altogether (Altmüller et al., 2001; Hauser and Boehnke, 1998). Epigenetic effects, parental-origin-specific effects, and epistasis can also hide the connection between genes and their phenotype, making it more difficult for re-searchers to detect variants associated with the disease (Altmüller et al., 2001; Ahlqvist et al., 2010).

Finally, T2D frequently has a late age of onset and a high population frequency, making it challenging to study using traditional genetic analysis methods (Hauser and Boehnke, 1998). In spite of all these convoluting factors, researchers have succeeded in identifying a number of gene mutations that are associated with different forms of diabetes and increase susceptibility to the disease (Altmüller et al., 2001; Hattersley et al., 2009; Perry and Frayling, 2008).

EXPERIMENTAL METHODS

The method traditionally used by researchers for locating genes implicated in human diseases is positional cloning (Altmüller et al., 2001). Positional cloning begins with the identification of a chromosomal region which is transmitted in families along with the disease phenotype. This is achieved by evaluating family units having affected members (for example, affected sibling pairs) with evenly spaced markers positioned across the genome. These markers are then compared to identify the chromosomal regions that consistently segregate with the disease (Hegele, 2001). Positional cloning is used to identify sequence variants from coding or controlling DNA segments associated with the disease phenotype (Altmüller et al., 2001). This method has helped to find the genes responsible for diseases that have simple Mendelian inheritance, such as cystic fibrosis (Zielenski and Tsui, 1995). However, the large amount of data generated from whole genome scans is difficult to synthesize and interpret for complex human diseases like diabetes.

Positional cloning studies have identified T2D susceptibility loci scattered all throughout the human genome. Unfortunately, only a few of these results could be reproduced in later experiments (Altmüller et al., 2001; Perry and Freyling, 2008). The difficulty in replicating experimental results indicates limitations in the linkage analysis techniques for multi-genetic diseases with multiple co-located independent susceptibility genes (Altmüller et al., 2001). Individual positional cloning studies have lacked the power to consistently identify specific gene loci associated with T2D, and this is likely related to the disease's genetic heterogeneity.

With the completion of the Human Genome Project in 2003, genome-wide association (GWA) studies have be-come the most popular and successful method used to identify genes and mutations associated with T2D (Perry and Freyling, 2008). Most GWA studies are non-hypothesis-driven and use brute force methods to analyze hundreds of thousands of single nucleotide poly-morphisms (SNP's) across the entire genome to find association with the disease phenotype (Perry and Frayling, 2008; National Human Genome Research Institute, 2011). The use of new technologies like DNA chips allow thousands of DNA samples

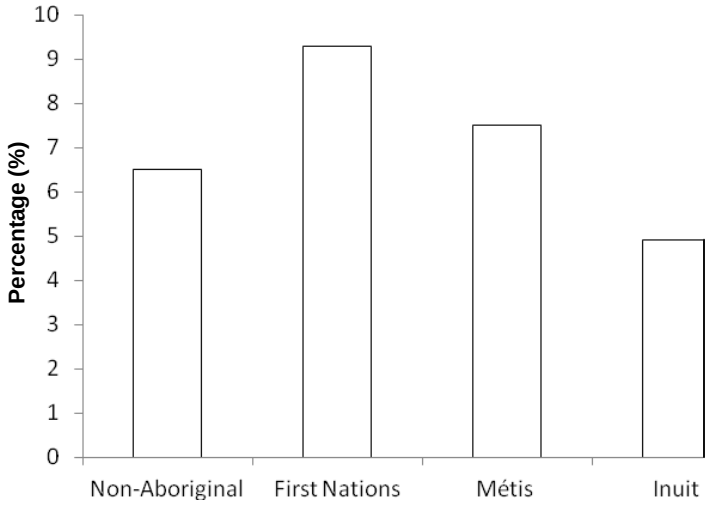

Figure 1. Percentage of Canadian individuals diagnosed with diabetes, organized by Aboriginal identity group, off- reserve population aged 20 and older.
Sources: Aboriginal Peoples Survey (2006), Canadian Community Health Survey (2007), cycle 4.1. (Garner et al., 2010).

INCIDENCE OF DIABETES AMONG ABORIGINALS AND NATIVE AMERICANS

Prevalence of diabetes in Canada and the United States

In 2006, it was estimated that approximately 2 million Canadians, equalling 6.2% of the total population, were living with diagnosed diabetes (Public Health Agency of Canada, 2009). At the same time, about 18 million people in the United States were living with diabetes, with one-third of these cases undiagnosed and 90 to 95% being T2D (Centers for Disease Control and Prevention, 2006). It is expected that one-third of American children born in the year 2000 will develop diabetes in their lifetime (Centers for Disease Control and Prevention, 2006).

Within Canada, the highest prevalence's of diabetes are found in the south, where a large portion of the Euro-Canadian population resides, making latitude a significant predictor of disease risk. In fact, age-standardized diabetes rates for Aboriginal populations in the Northwest Territories, the Yukon Territory, and British Columbia were lower than the national average (Szathmáry, 1994), with the Inuit being the only large group of Canadian Aboriginal people having diabetes prevalence rates lower than the rest of the country (Public Health Agency of Canada, 2003). The prevalence of diabetes among different Canadian groups is shown in Figure 1 (Garner et al., 2010).

Rising rates of diabetes among North American indigenous peoples

Not all North American indigenous people have shown higher morbidity for diabetes than European- or African-derived citizenry, however, this disease was rarely observed among Aboriginal populations prior to 1940 and its incidence has been clearly increasing since the 1960's (West, 1974; Young, 1993). This trend is evident among indigenous populations living in other parts of the world as well, including Micronesians and Polynesians (Zimmet et al., 1990), Australian Aborigines (O`Dea, 1991), and the people of Papua New Guinnea (Martin et al., 1980).

In the 1970's, a global health survey identified the emerging epidemic of T2D in North American Aboriginals (Young et al., 2000). This epidemic is simultaneous with rapidly rising rates of diabetes among the North American population in general (Figure 2), however, the disease is especially prevalent among a number of Canadian First Nations and Native American populations. Statistics from the First Nations Regional Longitudinal Health Survey (2002, 2003) have shown that Aboriginal women and men living on a reservation had about 4 times greater risk of death due to diabetes than other Canadian adults (Reading and Wien, 2005). Furthermore, diabetes rates in selected Aboriginal populations, including Algonquin reserves in north-eastern Quebec (Delisle and Ekoe, 1993) and Oji-Cree of Sandy Lake, in north-western Ontario (Harris et al., 1997) have reached up to 25% in all adults and 80% in targeted age groups.

Incredibly, the Oji-Cree people of northern Ontario have actually been recorded to show approximately 40% prevalence of T2D (Hattersley et al., 2009). This was over six times higher than the prevalence of T2D in the general Canadian population and was found to be the third highest prevalence recorded for any population in the world (Harris et al., 1997). Even more remarkably, diabetes was virtually non-existent as a medical diagnosis

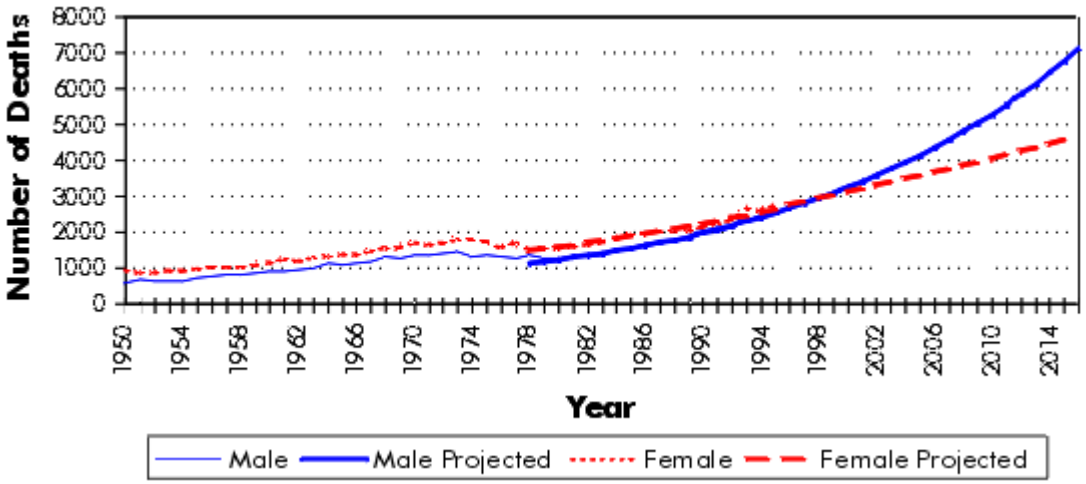

Figure 2. Number of Canadian diabetes deaths (1950 to 1995) and projections to year 2016, by gender. Projections based on deaths from 1978 to 1995. Source: LCDC (1998) - using Statistics Canada Mortality Data (Public Health Agency of Canada, 1999).

among this group; 70 years ago (Harris et al., 1997;

Young et al., 1990). The highest known rates of T2D in the world are found in the American population of Pima. Indians of the Gila River community in Arizona have, with an almost 20-fold increased incidence of T2D, compared to a typical American population (Knowler et al, 1978). The surprising prevalence of T2D among these indigenous populations suggests that these people carry some sort of endogenous susceptibility to the disease.

HYPOTHESES FOR DIABETES RISK IN INDIGENOUS POPULATIONS

Thrifty genotype hypothesis

The high morbidity of T2D among many Aboriginal populations appears to indicate a genetic predisposition to diabetes (Hegele, 2001). Because of the short time period involved and the size of the population affected (geographically and numerically), the genetic factors of this predisposition cannot reasonably be explained by recent mutations in the genomes of Aboriginal people. These gene variants must have been selected for (or at least, not selected against) a long time ago, when the gene-environment interaction resulted in an advantageous or neutral phenotype. One hypothesis which attempts to explain this situation is the thrifty genotype hypothesis.

The thrifty genotype hypothesis was first proposed in 1962 by population geneticist James V. Neel (1999). The theory behind the thrifty genotype is that populations native to North America had to genetically adapt to "feast and famine" conditions. These conditions would have resulted in the selection of alleles enabling the rapid Hyphen not necessary of insulin in response to rising glucose levels, thus facilitating fast storage of glucose as triglycerides (Neel, 1999). With modern conditions of relatively constant nutrient abundance and a high glycemic load diet, this physiological response became maladaptive, resulting in hyperinsulemia, insulin resistance, hyperglycemia, obesity and diabetes (Young et al., 2000). The thrifty genotype hypothesis is a fairly well accepted expla-nation for the observed differences in diabetes prevalence's between Aboriginal and non-Aboriginal people, and it has been cited frequently in literature (Young et al., 2000; Hegele, 2001; Hales and Barker, 1992; Norman et al., 1997; Poudrier, 2007). However, this theory has been criticized for a number of reasons.

A major point of contention rests in the assumption that carbohydrate food sources comprised a large enough portion of the traditional Aboriginal diet to justify a genetic adaptation. The hypothesis that the initial populating of the Americas occurred through migrations from north-eastern Asia, across Beringia and into north-western North America is well established in the scientific community (Stinson, 1992; Wendorf, 1989). This migration required the cold climate of the last ice age and meant that early Paleo-Indians, who would later populate the rest of the Americas, had to adapt to arctic and subarctic environments (Wendorf, 1989). Therefore, high plasma glucose levels would not have been a likely event during the early periods of migration to the Americas because the diet of these Paleo-Indians would have resembled the traditional diets of modern Inuit people. These diets are high in fat (83 to 88% of total calories) and protein (11 to 15% of total calories) but low in carbohydrates (0 to 2% of total calories) (Westman et al., 2007).

This first criticism would suggest that if the selection of "thrifty genes" occurred, it did not likely happen early in the populating of the Americas and was more likely to

develop when people began living in more moderate environments and were able to use agriculture for food production. These people would have had higher carbohydrate diets and were also more likely to experience the "feast and famine" conditions believed to be the stimulus for thrifty gene selection. However, it is important to note that these carbohydrates would have had a very low overall glycemic load compared to modern Western diets (Stinson, 1992). This means that the foods consumed did not create large elevations in plasma glucose levels and the resulting insulin spikes that are common with modern diets. Thus, if the hypothesis is true, we would expect to see more genes associated with diabetes and higher rates of T2D among Aboriginal populations living in moderate climates, where there were greater selective pressures for "thrifty genes", compared to populations living in contemporary arctic and subarctic regions. The differences in morbidity supporting this hypothesis have been observed in literature (as seen in Figure 1) (Public Health Agency of Canada, 2003), however, there are not yet any published studies comparing the prevalence of diabetes susceptibility genes between Inuit and southern Aboriginal populations.

Critics have also disputed the thrifty genotype hypothesis based on the fact that the survival advantage conferred by rapid insulin secretion, to avoid energy loss through glycosuria, would require insulin sensitivity in peripheral tissues to be maintained. This necessity would make the progression to T2D through the expression of "thrifty genes" unlikely and would require a different ultimate explanation for the recent increased susceptibility of indigenous populations to T2D (Reaven, 1998).

Due to the thrifty genotype hypothesis' apparent shortcomings, a number of modified and alternate explanations exist for the selection of genes which increase the risk of T2D when expressed in contemporary environmental conditions. One example, suggested by Szathmáry (1990), does not presuppose a diet which included excess carbohydrates. This theory better explains genetic adaptations to eating habits of early Aboriginal people living in arctic and subarctic regions, which would increase risk of T2D today. The hypothesis proposes that carbohydrate restriction and high levels of physical activity may have selected for individuals expressing high rates of gluconeogenesis and fatty acid metabolism. These traits can result in elevated resting plasma glucose levels when combined with modern high-carbohydrate diets and increase susceptibility to diabetes (Szathmáry, 1994).

If the genetic mutations increasing diabetes risk occurred this early on, both Inuit and First Nations people should be considered genetically at risk for T2D. The observed differences in prevalence rates between these groups would have to be explained by environmental factors like diet and physical activity levels, with Inuit people maintaining a more traditional diet and greater levels of physical activity, thus not expressing the disease phenotype as highly (Hegele et al., 2000a).

Thrifty phenotype hypothesis

First published in 1992 by Hales and Barker, the thrifty phenotype hypothesis attempts to describe the etiology of T2D without relying in genetic susceptibility. It suggests that inadequate fetal and early post-natal nutrition triggers physiological mechanisms of nutritional thrift. This results in greatly increased susceptibility to T2D later in life because of impaired development of the pancreatic endocrine tissues (Hales and Barker, 1992; Poudrier, 2007). The hypothesis asserts that proper nutrition at these early stages of development is critical for the growth of adequate supplies of pancreatic β-cells and their proper functioning. Reduced β-cell numbers have been observed as a result of protein insufficiency *in utero*, causing insulin deficiency and T2D by mid-adulthood (Hales and Barker, 1992). Like the thrifty genotype hypothesis, the thrifty phenotype hypothesis is supported by the observation of an inverse relationship between rates of Aboriginal diabetes in Canada and latitude (Young et al., 1990), because in locations with lower prevalence of T2D, average protein intake exceeds Euro-Canadian norms (Szathmáry et al., 1987).

SPECIFIC SUSCEPTIBILITY LOCI DETECTED IN ABORIGINAL PEOPLES AND NATIVE AMERICANS

Monogenetic forms of diabetes and the candidate gene approach

Due to the existence of multiple etiologic factors for T2D, the sensitivity and negative predictive value of gene mutations with identified association to diabetes are often low (Hegele, 2001). However, genetic studies have been very successful at identifying the causes of monogenic forms of diabetes (Altmüller et al., 2001). These types of diabetes are the result of inheritance or spontaneous occurrence of a mutation or mutations in a single gene; they are distinct from type 1 and type 2 diabetes and are very rare (Hattersley et al., 2009; Perry and Freyling, 2008).

Neonatal diabetes and diabetes diagnosed within the first six months of life appear to be commonly produced by single gene mutations, with different genes being associated to different subgroups of diabetes. For example, transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM) are often associated with an abnormality in imprinting of *ZAC* and *HYMAI* genes on chromosome 6q, and mutations in the *KCNJII* gene, respectively. In their publication, Hattersley et al. (2009) listed other genes which cause these monogenic forms of diabetes; with the most common mutation resulting in maturity-onset diabetes of the young (MODY) being in the HNF-1α gene (MODY3).

The HNF-1α gene is located at chromosome 12q24 and is expressed predominantly in the liver and kidneys (Winter et al., 1999). Specific mutations in this gene result in the non-insulin dependent diabetes mellitus type I, which is inherited as a monogenic autosomal dominant trait (National Center for Biotechnology Information, 2011). Genes identified in monogenic forms of diabetes, such as HNF1-α, are useful for candidate gene methods of searching for mutations associated with T2D. This is because of the known importance of their products in normal insulin secretion and sensitivity (Perry and Freyling, 2008).

The Oji-Cree of sandy lake, Ontario

Hegele et al. (1990) studied the Oji-Cree of sandy lake in Northern Ontario using positional cloning and the candidate gene approach to identify susceptibility loci for T2D. Candidate genes were chosen based on the known role of their products in carbohydrate and insulin metabolism. HNF-1α was studied as a candidate gene and a novel missense mutation (HNF-1α G319S variant) was found. The diabetes phenotype associated with this mutation did not resemble MODY (maturity-onset diabetes of the young), and was instead characterized by obesity and insulin resistance (Hegele, 2001). This indicates that the insulin secretion defect in HNF-1α S319 carriers is less severe than the HNF-1α mutations of MODY3 and the defective function of HNF-1α S319 is therefore, not uncovered until obesity-related insulin resistance begins to develop (Busch and Hegele, 2002).

Both HNF-1α S319/G319 heterozygotes and HNF-1α S319/S319 homozygotes showed significant odds ratios for having T2D when compared to the normal HNF-1α G319/G319 genotype (1.97 and 4.00, respectively; with 95% confidence interval) (Hegele et al., 1990). It was found that the HNF-1α S319 allele was associated with about 40% of the cases of T2D in Sandy Lake and about 20% of additional cases were accompanied by the PPARG A12 allele, which was also strongly associated with T2D (Hegele et al., 2000b). The absence of the HNF-1α G319S SNP (single nucleotide polymorphism) in other human populations suggests that his mutation is specific to the Oji-Cree. The HNF-1α G319S mutation is one of the most specific genetic tests for T2D ever described in any population (Hegele et al., 2000a). It showed consistent statistical association with T2D (97% specificity for Oji-Cree patients of age 50 or more). It had the ability to act as a predictive test for disease susceptibility (95% positive predictive value for Oji-Cree patients' age 50 or more) and was predictive of the clinical severity of diabetes (Hegele et al., 2000a). Further studies of the sandy lake First Nation, involving larger population sizes, have confirmed the greatly increased risk of T2D for carriers of HNF-1α S319 (Ley et al., 2011). More recently, genome-wide significance has been confirmed for HNF1A variant association with T2D through large-scale association analysis (Voight et al., 2010).

Another interesting discovery in this in the Oji-Cree was the functional R230C variant of the ABCA1 gene. First described in the population for its association with low plasma HDL-C cholesterol level, it is also a factor that can be associated with the development of T2D (Wang et al., 2000; Fagot-Campagna et al., 1997). Its role in T2D risk requires further analysis; however, it is a common variant exclusive to Native American and descent populations. Its presence in both North and South American Aboriginal populations and its potential positive effect on intracellular cholesterol and energy storage make this allele a possible candidate for Neel's hypothesis, probably arising early on founder populations of Beringia (Hegele et al., 1990).

The Pima Indians of Gila river, Arizona

Similar to the Oji-Cree of sandy lake, the Pima Indians of the Gila River community show very high rates of T2D (almost 20-fold increased incidence of T2D compared to a typical American population and the highest reported prevalence of T2D of any population in the world). This has attracted the attention of researchers determined to identify gene variants associated with T2D. A productive long-term relationship between researchers and the Pima Indians has allowed for over 25 years of study into the causes of T2D in this population (Knowler et al., 1978). A number of different gene SNPs sequenced in Pima Indians of Arizona, as well as replicated variants from Caucasian genome-wide association (Caucasian GWA) studies, have been evaluated for association with T2D among this group and some other Native American populations (Nair et al., 2012; Rong et al., 2009; Guo et al., 2007; Bian et al., 2010; Muller et al., 2010; Dong et al., 2011). Most of the associations have been modest, with a few being statistically significant. However, variants of these genes have not yet been described as major risk factors for T2D in this population. So far, no gene variants known to this author have been identified in the Pima Indians that have had similar strength of association to T2D as the HNF-1α G319S variant in the Oji-Cree. The major gene or genes responsible for the extremely high incidence of T2D in this community remain unknown.

Confirmed type 2 diabetes genes

There are currently over 35 independent loci identified through linkage analysis and GWA studies that show significant genome-wide associations with T2D (Voight et al., 2010). This is up from only 18 confirmed genes associated with T2D in 2008 (Perry and Freyling, 2008) and at least one of these variants, G319S of HNF1α, was specific

to a North American Aboriginal population (Hegele et al., 1999). In spite of the numerous discoveries made through GWA studies, currently known variants account for only 10 to 15% of the estimated overall heritability of T2D (Garg, 2011). This is less surprising, considering the small effect sizes of most of the variants identified so far, ORs ranging from 1.1 to 1.3 (Ahlqvist et al., 2010).

Of the genes identified for association with T2D, TCF7L2 has the strongest effect, with a pooled OR of 1.46 for the rs7903146 polymorphism (Cauchi et al., 2007; Cruz et al., 2010). Evidence from meta-analysis has suggested that variants of the TCFL2 gene are involved in about 1/5 of all T2D cases (Tong et al., 2009). Variants at this loci have consistently shown strong association with T2D in many populations (Grant et al., 2006; Mayans et al., 2007; Marzi et al., 2007; Humphries et al., 2006; Vliet-Ostaptchouk et al., 2007; Cauchi et al., 2006; Damcott et al., 2006; Scott et al., 2006; Zhang et al., 2006; Groves et al., 2006; Florez et al., 2006; Chandak et al., 2007; Horikoshi et al., 2007; Hayashi et al., 2007) but TCF7L2 was not found to have a significant association with T2D risk when studied in Pima Indians (Gou et al., 2007). Because most of the previously identified variants are only responsible for small effects in Caucasian populations, the sample sizes from Aboriginal groups must be fairly large in order to provide sufficient power for detecting or excluding their association with statistical significance (Mayans et al., 2007). Perhaps the variants found from GWA studies of Caucasians are responsible for modest increases in T2D susceptibility in North American Aboriginals. But, due to the smaller size of sample populations, the statistical power of these studies has been mostly insufficient to confirm gene association with confidence (Rong et al., 2009).

Additionally, some of the polymorphisms robustly associated with T2D have shown substantial allele frequency differences between population groups (Hayashi et al., 2007; Parra et al., 2007). Loci identified in large GWA studies of Caucasian populations may not have single-nucleotide polymorphisms (SNPs), important to disease risk in Aboriginal groups. This is because low frequency variants which cannot be detected in Caucasian populations may be major factors in disease risk for other populations with different allele frequencies. Thus, genes responsible for T2D risk in Caucasians, which are often used to search for potential SNPs associated with T2D in other populations, may not necessarily be major factors in disease risk for Aboriginals.

The molecular mechanisms responsible for the increased susceptibility associated with many of the confirmed variants remain obscure (Voight et al., 2010). However, a large amount of the known genetic risk for T2D appears to be related to beta cell dysfunction. This is because majority of the identified gene variants associated with increased T2D risk seem to affect insulin secretion (as opposed to other risk factors like insulin resistance or excess hepatic glucose production) (Ahlqvist et al., 2010; Voight et al., 2010; Rong et al., 2009).

CLINICAL BENEFITS OF GENETIC RESEARCH FOR DIABETES IN INDIGENOUS POPULATIONS

According to Statistics Canada, over 1 million people identified themselves as Aboriginal, Métis, or Inuit in the 2006 Census of Population. In the United States, over 5 million identified themselves as American Indian or Alaska Native in the 2010 census (Norris et al., 2012). Between 1996 and 2006, the Canadian Aboriginal population grew at a rate of 45%, much faster than the non-Aboriginal population, which grew at a rate of only 8%. The Aboriginal diabetes epidemic affects a very large number of North Americans and this number is expected to increase. The median age of the Canadian Aboriginal population (27 years) is also lower than that of the rest of the Canadian population (40 years), indicating rises in the proportion of Canadians with diabetes, as these individuals age (Statistics Canada, 2010).

Diagnosed diabetes is known to shorten life expectancy by about 9 years and increase the number of visits to physicians and specialists by about two times compared to individuals without diabetes. Diabetes also dramatically increases the number of hospitalizations for limb amputations, cardiovascular disease and other major complications (Public Health Agency of Canada, 2008). The incidence of coronary heart disease, a condition commonly caused by diabetes, of Northern Ontario Aboriginals has tripled in the two decades between 1980 and 2000; it is now four times more prevalent than in the general population of Ontario (Shah et al., 2000). Finding new ways to prevent and treat T2D (and its complications) will help to decrease the overall burden of this disease on health care systems and is certainly in the interest of medical science.

Research into the molecular basis of this complex human disease has allowed for the identification of genes associated with a number of clinical subgroups of diabetes and has helped to explain some of the phenotypic heterogeneity of the disease for variables such as age of onset and severity (as in the case of monogenic forms of MODY) (Lillioja and Wilton, 2009; Busch and Hegele, 2002; Hattersley et al., 2009; Hegele, 2001; Hegele et al., 1999). With the few T2D susceptibility loci currently identified, geneticists and molecular biologists can now begin to determine the mechanisms by which these genes influence disease risk. Improving our understanding of T2D pathogenesis will also improve our methods of treating or possibly curing its different forms.

Genetic tests remain fairly expensive and their clinical use should presently be limited to individuals who show characteristics of strong genetic etiology for their disease. For example, this includes patients who have familial diabetes with an affected parent or diabetes diagnosed within the first 6 months of life (Hatterskey et al., 2009).

When genetic testing becomes more available, identifying individuals who are at risk of developing T2D can give healthcare providers an idea of the probability of disease onset years before its clinical appearance in a patient, and allow for the selection of treatments most likely to be effective for that particular form of the disease (Poudrier, 2007). This kind of personalized medicine through genetic diagnosis is already possible for specific groups of people like the Oji-Cree, however, the identification of these genes in individual patients does not yet offer much improvement in strategies for treating T2D (Diabetes Genetics Initiative, 2007).

Until these diagnoses become economically feasible, all Aboriginal people should consider taking precautions to the development of T2D (or steps to reduce the severity of existing T2D). This includes, for example, weight reduction (with reduces insulin resistance) and consuming a more traditional diet or maintaining a high level of physical activity (as suggested by the thrifty genotype hypothesis) (Surwit and Schneider, 1993; Hegele et al., 1999). In Australian Aborigines, these preventative measures had the effect of normalizing plasma glucose and insulin levels in individuals with T2D (O`Dea, 1991). These lifestyle changes, therefore, have had documented benefits in other indigenous populations suffering from high rates of T2D and are some of the best methods presently available for reducing diabetes risk.

ENVIRONMENTAL FACTORS INFLUENCING DIABETES IN INDIGENOUS PEOPLES AND SOCIAL ISSUES INVOLVED WITH RESEARCH

Lifestyle and stress

Of the environmental component influencing T2D, the most is lifestyle (Szathmáry, 1994). Lifestyle includes the variable nutrition governed by access to food and cultural eating behaviours, as well as differing levels of activity or energy expenditure between groups of people. Changes in the typical lifestyle of Aboriginal people, from one which was characterized by high levels of physical activity to one which is much more sedentary, have been evident in the past few decades (Hegele, 2001). Studies of Pima Indians have shown elevated rates of T2D in individuals reporting low levels of leisure-time physical activity in their past, a common characteristic among diabetics (Kriska et al., 1993). Many other Aboriginal populations have also demonstrated reduced physical activity in recent years (Young et al., 2000; Hegele, 2001; Norman et al., 1997). It is highly likely that the lifestyle changes among Aboriginal peoples in the past few decades have favoured the emergence of T2D in genetically susceptible individuals and have played a large part in the current disease epidemic (Szathmáry, 1994).

Diet and exercise may not be the only environmental factors which can increase the risk of diabetes; stress may contribute significantly to the pathophysiology of T1D and T2D as well. Stress hormones such as cortisol generally have a hyperglycemic effect, elevating blood plasma glucose through hepatic glucose production, while at the same time reducing glucose utilization by the tissues and increasing lipolysis (Surwit and Schneider, 1993). These mechanisms have clear adaptive benefits in energy mobilization for healthy individuals experiencing stress; however, they become problematic when glucose metabolism is compromised, as in the case of diabetics (Surwit and Schneider, 1993). Sustained elevation of cortisol (an adrenal stress hormone) has also been implicated in the development of abdominal obesity and hyperinsulinemia (Bjorntorp, 1991). Abdominal obesity, also known as central or upper body obesity, is predictive of T2D (Hales and Barker, 1992). Few or no studies have been conducted to identify the relationship between stress and T2D in North American Aboriginal populations; however, it has been hypothesized that individuals exposed to chronic stress may be predisposed to both central obesity and diabetes (Bjorntorp, 1991).

Socioeconomic factors

Recent studies have cast doubt on the thrifty genotype hypothesis's explanation for T2D risk in indigenous people of the Americas (Campbell et al., 2012). Evidence is beginning to support the possibility that differences in T2D prevalence between ethnic groups may be better accounted for by environmental factors than population differences in risk allele frequencies at T2D susceptibility loci (De Ferranti, 2004). A study by Iwasaki et al. (2004) examining sources or stress for Aboriginal peoples suffering from diabetes in Manitoba, Canada identified a large number of individuals as living in marginal economic conditions. From interviews conducted in two Anishnaabe communities of Ontario, Canada, one participant stated: "I think the worst part of it, why people are overeating and not looking after themselves is lack of employment, lack of services, and lack of housing." (Sunday et al., 2001)

This suspicion is supported by Statistics Canada surveys which show Aboriginal people of core working age (25 to 54 years) having 16% lower employment rates than non-Aboriginals (this difference is about twice as large for Aboriginal people living on reservations). In the same age group, the median total annual income of the Aboriginal population was $22,000, which was much lower than the non-Aboriginal population median income of $33,000, with only $14,000 for First Nations people living on a reserve (Statistics Canada, 2010). In 2006, 29% of First Nations people and 45% of individuals on a reserve lived in a home in need of major repairs. A much lower proportion (7%) of non-Aboriginal people were identified as living in homes in need of major repairs (Statistics Canada, 2010). Surveys have also shown that Aboriginal children are more likely to live in large families and live solely with their grandparents. First Nations and

Inuit people are less than half as likely as non-Aboriginals to have a university degree but are more than twice as likely to have less than a high school education. Furthermore, Aboriginal adults are remarkably overrepresented in the Canadian prison population (comprising only 3.1% of the adult population; however, representing 25% of adults admitted to provincial/territorial prisons and 18% of adults admitted to federal prisons in 2007 to 2008) (Statistics Canada, 2010). Finally, a 2004 survey identified Aboriginal people as over three times more likely than their non-Aboriginal counterparts to have been violently victimized in the past year (Statistics Canada, 2010).

All of these statistics point to more stressful living conditions for Aboriginal people and thus an environment of increased risk for T2D. The difference in diabetes prevalence among the Aboriginal and non-Aboriginal populations may be much less surprising when viewed in light of these dramatic differences in their lifestyles and living conditions. Socioeconomic status (SES) has been demonstrated to strongly predict disease risk, with low SES being associated with significantly higher disease risk (Florez et al., 2009). Highly significant correlation between Native ancestry and socioeconomic status (SES) (lower SES correlated with greater Native American ancestry) has been demonstrated in other countries as well, and may help to explain the concurrent significant correlation between Native ancestry and increased rates of T2D (Campbell et al., 2012; Waters et al., 2010). These environmental factors suggest that the actual genetic component of susceptibility to diabetes may be less than originally expected.

When considering variables in epidemiological studies, a great deal of attention is often given to race with the exclusion of other complex and important variables associated with chronic disease. Some of these variables include social class, level of marginalization in society, poverty, lifestyle, and living conditions (Poudrier, 2007). Considering environmental factors in the design of gene studies for T2D may help to increase the power for finding real genetic determinants of the disease by accounting for other major sources of variation associated with the disease onset. It should be noted that racial and geographical grouping of populations should not therefore be discarded; these are some of the few methods available to researchers for separating genetic risk factors among populations in a visible way.

Social issues of searching for type 2 diabetes genes in Aboriginal or Native American populations

There are definite considerations to be made concerning the implications of including race as a genetic risk factor in health discourse. For a group of people who have historically been viewed by the dominant Western society as inferior, searching for biological evidence which may support this idea should be done with care. Researchers must also be cautious not to allow the search for diabetes susceptibility genes to divert attention from important known environmental risk factors facing Aboriginal people in this multi-factorial disease. Finally, researchers must be aware of the terminology they use (for example, First Nations, Métis or Inuit) when describing Aboriginal populations and should avoid over generalizing their conclusions. The indigenous people of North America are both genetically and culturally diverse and this needs to be kept in mind when searching for T2D susceptibility genes.

Conclusions

Understanding the etiology of T2D in North American Aboriginal people has been a challenge for researchers. In spite of great efforts to identify susceptibility loci associated with T2D and other complex human diseases, the specific genetic causes remain to be clearly defined (Altmüller et al., 2001). Only a fraction of the genetic variability associated with T2D can be explained with currently identified susceptibility genes and it is clear that there are still many genes associated with this disease that remain to be found (Lillioja and Wilton, 2009; Perry and Freyling, 2008). Future genetic discoveries will likely hinge on improvements in genetic technologies and studies involving larger populations to find statistically significant results (Altmüller et al., 2001). Further meta-analysis of past GWA studies and the analysis of additional forms of genomic variation (other than SNP's), such as copy number variants (a form of structural variant which is not detected in GWA studies but has known roles in other human diseases) may also help to identify T2D disease loci in the future (Perry and Freyling, 2008).

Modern large-scale GWA studies provide the opportunity to identify completely unexpected genes that are associated with T2D and an understanding of these genes and the function of their products will broaden our awareness of the chemical pathways associated with T2D (Perry and Freyling, 2008). There is great potential for improvement of our knowledge of the pathophysiology of complex human diseases such as T2D through genetic research.

More specific studies of Aboriginal populations will be important for identifying possible "thrifty genes" that are responsible for the current epidemic in T2D among these people. It is unlikely that the identification of a single gene variant will solve this mystery. As was demonstrated by the discovery of the HNF-1α GS319S variant specific to the Oji-Cree, the Aboriginal population should not be viewed as racially or genetically homogeneous (Poudrier, 2007; Hegele et al., 1999). This means it is unlikely that the same T2D risk alleles will be identified in all Aboriginal groups. Any mutations responsible for increased risk of T2D will probably only be present in specific population groups, and identifying these groups

requires a historical understanding of Aboriginal people with reference to their genetic background and how populations moved or merged as a result of European colonization.

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Full Length Research Paper

Prevalence of hyperglycaemia, obesity and metabolic syndrome (a three component study) among hospital personnel in the Littoral Region of Cameroon

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There is evidence worldwide of the high prevalence of obesity, hyperglycemia and metabolic syndrome in health care providers, although very scanty data is available on this in sub Saharan Africa. The present study aims to determine the frequency of diabetes, elevated Body mass index (BMI) and metabolic syndrome among health-care workers in some hospitals and clinics in Douala, Cameroon. An observational and cross-sectional study was done for the diagnosis of metabolic syndrome. The 2005 definition of The International Diabetes Federation (IDF) was used for 147 health workers. Data were grouped and analyzed according to gender and age. 7.5% of the hospital workers had metabolic syndrome, 71.2% were at high risk of developing metabolic syndrome because of elevated abdominal obesity, 38.4% were obese (BMI ≥ 30) and 4.8% had elevated blood sugar levels. The prevalence rate increased with age: 2.9% (18 to 36 years), 9.5% (37 to 55 years) and 50% for more than 56 years. The definition gave the highest prevalence rate of 7.5% while the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) gave 0.7% with the World health organization (WHO) (1999) giving the lowest prevalence rate of 00%. There is a high prevalence of obesity and metabolic syndrome among health care personnel in the Littoral region of Cameroon. It is imperative to implement programs to screen these risk factors by means of routine medical exams and improving the lifestyles of Cameroonian health care workers. These study findings could be the basis for future research among hospital staff and the general population.

Key words: International Diabetes Federation (IDF), hyperglycemia, metabolic syndrome, body mass index.

INTRODUCTION

Metabolic syndrome is a cluster of disorders including raised blood pressure, cholesterol and blood sugar which increase the risk of cardiovascular disease and diabetes. Metabolic syndrome is a constellation of risk factors that predisposes the individual to coronary artery disease, stroke and diabetes. The metabolic syndrome has been intensely studied in many Western countries but relatively less in sub-Saharan Africa. The prevalence of the key determinants of metabolic syndrome (like hypertension, diabetes, elevated body mass index (BMI), dyslipidemias and central obesity are on a steady rise probably due to westernization of diets and adoption of more sedentary lifestyles, all favoured by an urban to rural migration (Rees et al., 2007). Currently, the most popular criteria for MS diagnosis is the International Diabetes Federation (IDF 2005) consensus definition (Phengtham, 2011). There is evidence worldwide of the high prevalence of these pathologies in health care providers (Garrido et al., 2009). The prevalence of metabolic syndrome (MS) among health employees has been reported to be above the figures for the general population (Padierna-Luna et al., 2007).

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Hospital work requires day and night shifts which, together with work stress, could lead to an increased incidence of MS (Vitaliano et al., 2002; Karlsson et al., 2001). Whichever definition is used, the presence of MS is associated with a doubled risk of cardiovascular disease (CVD) (Dekker et al., 2005; Isomaa et al., 2001) and especially stroke (Hsin-Jen et al., 2006) and type 2 diabetes mellitus (T2DM) (Wannamethee et al., 2005).

Health care workers have a high prevalence of MS. In South America, about a third of nurses had High blood pressure (HBP) and 16.6% were obese (Leão de Aquino et al., 2001) while 26% of all health workers had HBP (Mion et al., 2004). In Europe, there was a high prevalence among doctors of components of MS and a greater risk than the general population of developing any form of CVD (Nakládalová et al., 2005). In the USA, a large increase in the components that constitute MS was found in doctors, as part of the Physician's Health Study (PHS). Of the total of 22,046 doctors, 354 presented with >3 metabolic changes at the beginning of the study, reaching 2,050 at the end of the observation (Stürmer et al., 2006).

The global prevalence of chronic non communicable diseases (NCDs) is on the rise, with the majority of the growth occurring among populations in developing countries (Murray and Lopez, 1997). The quickening pace of change and adoption of western lifestyles by people in developing countries has led to a sharp rise in the incidence of systemic diseases such as diabetes, cancer, coronary artery diseases and hypertension. In sub-Saharan Africa, NCDs are projected to surpass infectious diseases by 2030 (Mathers and Loncar, 2006; Yach et al., 2004). Yet epidemiological studies of these conditions using validated methods are rare especially in Central Africa; besides, knowledge about this rampant clinical entity is meager not only among the general population but also among healthcare providers. Thus the world is currently going through a silently damaging epidemic. The aim of this study was to determine the prevalence rate of obesity, hyperglycemia and metabolic syndrome (MS) among health workers in Douala Cameroon.

MATERIALS AND METHODS

Sampling technique

Sampling was purposive because the study targeted adult (age 18+) health workers of urban and peri-urban areas of the Littoral Region. Sampling was clustered because participants were sampled at the level of specific chosen locations, notably the district hospital or other health center found at the sampled health district. Sampling was randomized because it was by chance that a health worker could be working on the shift during which the research team was around. In summary, purposive-clustered-randomized sampling was used for this study.

Study area

The study area is the coastal area of Cameroon (Douala the commercial capital and the districts in the peri-urban zone), where the main activity in the urban area is commerce and other sedentary occupations as opposed to the peri-urban area where the main activity is farming, with the inhabitants having a relatively more physically active lifestyle. The climate in both the urban and peri-urban areas is warm and humid. Hospital personnel were recruited from the district Hospitals of Deido, New Bell, Cite des Palmiers, Nylon, Bonassama and Polyclinic Bonanjo Annexe, all in the Douala municipality.

Participants and recruitment

A cross sectional survey was conducted using hospital personnel of the district hospitals in urban region of littoral region of Cameroon. Data were collected from all personnel who voluntarily attended the medical examination on the designated days. Participants with incomplete data were excluded. The exact recruitment criteria included: Age 26 to 56 years, overnight fast and sex. Both male and females were recruited for the study. Excluded from this study were pregnant women, personnel who are nonfasting or refused to participate in the study, or refused to sign the consent form. Those arriving the hospitals after 12.30 noon were advised to report the next morning after an overnight fast. A total of 147 healthcare workers of both sexes with ages between 26 to 56 years were recruited for this study between May 2010 and April 2011. A prior pilot study was conducted at the Douala Cardiovascular Center (a specialized center in the treatment of most of the determinants of MS) in order to ascertain the competence of the trained personnel and the validity of the instruments to be used.

Measurements

Trained certified medical personnel obtained blood pressure and anthropometric measurements (height, weight, waist and hip circumferences) and collected a venous blood sample for measurement of glucose. Waist circumference was measured with a spring-loaded measuring tape, midway between the inferior angle of the ribs and the superior iliac crest at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm, whereas hip circumference was measured at the outer most points of the greater trochanters. Waist to Hip Ratio (WHR) was recorded to the nearest 2 decimal places. Fasting blood sugar concentration was measured using an enzymatic reaction (glucose oxidase method). Questionnaires on medical and medication history as well as lifestyle options (area of residence, dietary habits, sporting activities, occupation, alcohol consumption, sleep patterns and consumption of rapid sugars) were administered to all the subjects.

Metabolic syndrome designation

This was a three component metabolic syndrome study. Prevalence of the metabolic syndrome and its components were estimated using the 2005 definition of IDF which was the main definition used for the study. This prevalence rate was then compared with those of the other definitions (NCEP-ATP III (2002) and World Health Organization (WHO) (1999). The determinants or components of metabolic syndrome considered in this study were: Body mass index (BMI), Waist /Hip Ratio (WHR), elevated blood sugar, waist circumference (WC) and hypertension (HT).

Statistical methods

Data from the questionnaires and laboratory reports were entered into an electronic data base Epi-Info 6.04d (CDC, 2001). Range and

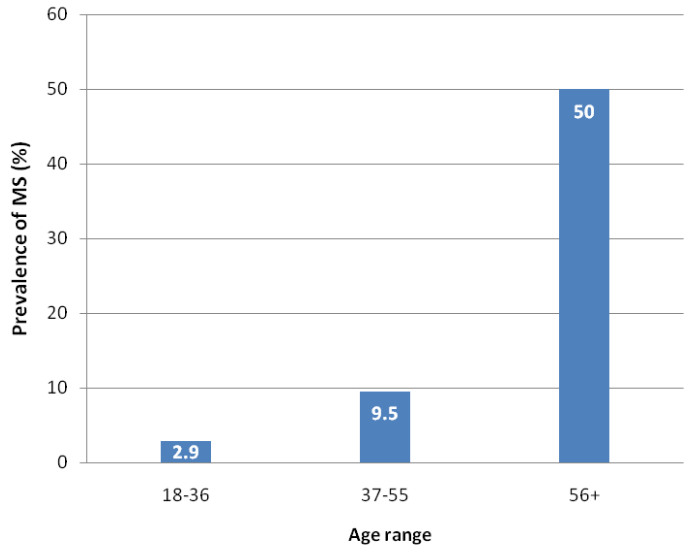

Figure 1. Prevalence of MS using IDF (2005) definition among hospital personnel stratified for age (years).

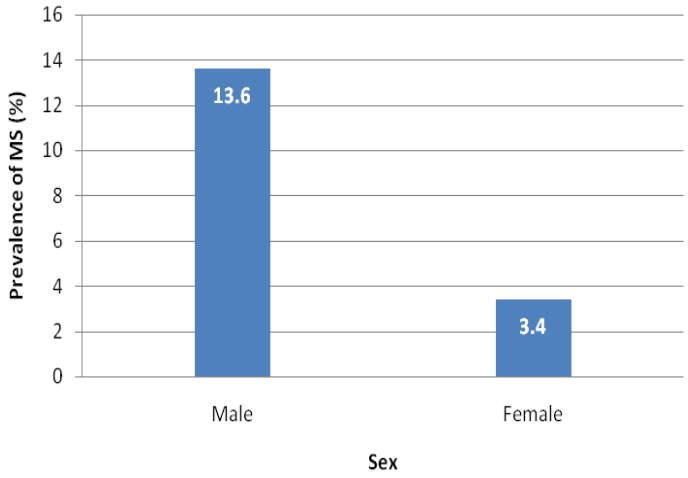

Figure 2. Prevalence of MS according to the gender.

consistency checks were used to minimize data entry errors. Data were merged and exported from Epi-Info to Statistical Package for the Social Sciences (SPSS).

Generating computed variables

To answer specific indicators, some variables were derived from 'raw variables' using direct compute command or command syntax such as the generation of the BMI from height and weight of the patient.

Development of syntax journal

A syntax journal was developed for each major steps of the analysis. Syntax was also indispensable to solve specific problems that could not be done using direct interactive-window analysis. For categorical variables, descriptive statistics was used to present the distribution of subjects between and within subsets using frequencies and proportions. Associations between lifestyle options and determinants of the metabolic syndrome was done using χ^2-test chi-square test for categorical variables with 95% confidence interval ($p < 0.05$). .

Ethical considerations

The study protocol was approved by the National Ethics Committee of the Ministry of Public Health, Cameroon as well as administrative clearance from the Authorities of the Littoral region. All subjects gave informed consent to participate and the authors followed the Declaration of Helsinki on biomedical research involving human subjects.

RESULTS

About 46.9% of these personnel were of the youthful range (26 to 36 years), 50.4% were aged between 37 and 55 years, with only 2.7% aged more than 56 years. This group had more females (59.9%) than males (40.1%). Elevated waist circumference was the most prevalent component while the diabetic condition was least prevalent. The highest prevalence rate for MS was amongst those medical personnel aged more than 56 years (Figure 1). Those aged between 26 to 36 years expectedly registered the lowest MS prevalence rate. The males recorded higher prevalence rate than the females (Figure 2). The IDF (2005) definition gave the highest prevalence estimate (7.5%) (Figure 3 and Table 1). No significant difference (Table 3) was found between the MS prevalence rate among the different health districts.

DISCUSSION

This study revealed a prevalence rate of 7.5% for the metabolic syndrome amongst the hospital personnel in the Littoral Region of Cameroon. In another study in Celaya, Guanajuato, involving 142 women (71%) and 58 men (29%), with a mean age of 41 years (range 19 to 59), the overall MS prevalence was 29.5% (Padierna-Luna et al., 2007) which is much higher than the 7.5% prevalence rate reported in this study. Similar studies in Parkistan (Alam et al., 2011) and Lampang hospital (Phengtham, 2011) revealed higher rates of 14.95 and 9.5%, respectively. Our findings are also relatively much lower when compared to the staggering 34% metabolic syndrome prevalence rate reported for hospital workers in Botswana (Garrido et al., 2009). In another study conducted in Ethiopia (Tran et al., 2011), using the NCEP/ATP III and IDF definitions, the overall prevalence of MS was 12.5 and 17.9%, respectively (Tran). This is quite different from the results from this study which gave prevalence rates of 0.7 and 7.5%, respectively using the NCEP/ATPIII and the IDF (2005) definitions (Table 2).

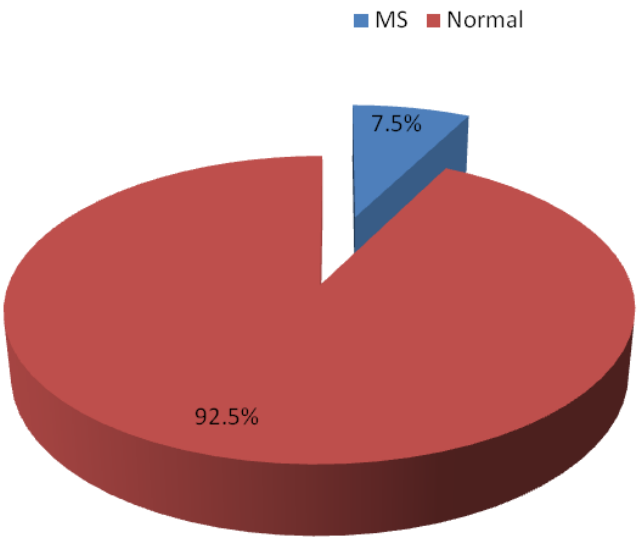

Figure 3. Prevalence of MS among hospital personnel using the IDF (2005) consensus definition.

Table 1. Prevalence of determinant of MS among the medical personnel.

Indicator of metabolic syndrome	Frequency	LB (95% CI)	Percent	UB (95% CI)	N
Elevated blood sugar	7	1.9	4.8	9.6	147
Hypertensive condition WHO	29	13.6	19.7	27.1	147
High BMI ≥30	56	30.4	38.4	46.8	146
Elevated WHR	54	29.2	37.0	45.4	146
Hypertensive condition (NCEP/ATP III)	48	25.2	32.7	40.9	147
Elevated Waist circumference (NCEP/ATP III)	67	37.6	45.9	54.3	146
Elevated waist circumference IDF (2005)	104	63.2	71.2	78.4	146

LB = lower bond [lower limit]; UB = upper bond [upper limit]; CI = confidence interval; N = sample size, BMI = body mass index; hypertensive condition (WHO) = hypertensive condition according to the WHO (1999) definition of MS; WHR = waist to hip ratio; NCEP/ATPIII = National Cholesterol Education Program-Adult Treatment Panel III, IDF (2005) = International Diabetes Federation, 2005 definition of metabolic syndrome; FBS = fasting blood sugar, MS = metabolic syndrome.

Table 2. Prevalence of metabolic syndrome using the different definitions.

Definitions used	Frequency	LB (95% CI)	Percent	UB (95% CI)	N
Metabolic syndrome with BMI and/or WHR WHO 1999	0	0.0	0.0	2.5	147
Metabolic syndrome with BMI only	0	0.0	0.0	2.5	147
Metabolic syndrome with WHR only	0	0.0	0.0	2.5	147
Metabolic syndrome using NCEP ATP III	1	0.0	0.7	3.7	147
Metabolic syndrome using IDF (FBS≥1.26 g/l)	2	0.2	1.4	4.8	147
Metabolic syndrome using Consensus IDF definition (FBS at 1.0 g/l)	11	3.8	7.5	13.0	147

The risk of developing MS is strongly associated with night-shift work in nurses. Medical counseling should be promptly instituted in night-shift workers with the syndrome and in case of persistence or progression, a change in work schedule should be considered (Pietroiusti et al., 2010). This study shows that MS increases with age, with the most affected age group being 35 to 56 years and those above 56 years showing

Table 3. Prevalence of MS (FBS at 1.0 g/l) in different Health districts.

Health district	Metabolic syndrome IDF (FBS at 1.0)		Total n (%)
	Absent n (%)	Present n (%)	
Deido	21 (91.3)	2 (8.7)	23 (100.0)
New Bell	45 (91.8)	4 (8.2)	49 (100.0)
Nylon	7 (87.5)	1 (12.5)	8 (100.0)
Polyclinic Bonanjo	63 (94.0)	4 (6.0)	67 (100.0)
Total	136 (92.5)	11 (7.5)	147 (100)

$\chi 2$ -test: 0.594; DF = 3; P = 0.898.

the highest prevalence rate. This is consistent with the findings of other investigators (Phengtham 2011; Garrido et al., 2009). The males in this study showed a higher prevalence rate than the females and this is different from those reported in healthcare workers in Parkistan (Alam et al., 2011) and in Botswana where the female gender instead was strongly associated with obesity and metabolic syndrome. The very high pre-valence rate of obesity and metabolic syndrome may suggest that hospital staffs are quite complaisant when it comes to taking annual health check-ups. Such check-ups may show early stages of intermediate MS and remind staff to control their lifestyle (Patrakitkomjorn et al., 2011). Moreover a longitudinal study suggested that a three year period suffice for healthy healthcare workers to develop the components of the metabolic syndrome (Patrakitkomjorn et al., 2011). It has been suggested that at least one measurement from each of these components namely anthropometric, blood pressure, glycemia and dyslipidemia is adequate to diagnose MS (Khalil et al., 2011). This makes it much easier for the hospital personnel to have an indication of the metabolic syndrome components already being harbored by them.

As far as the components of the metabolic syndrome are concerned, using the IDF (2005) definition, hyperglycemia gave the lowest prevalence rate while central obesity (elevated waist circumference) showed the highest prevalence. This is consistent with results obtained from other studies, although another recent study suggests that even neck circumference could also be included in the anthropometric measurements for the diagnosis of the metabolic syndrome (Khalil et al., 2011).

A sedentary work schedule and lifestyle with their lowering effect on the resting metabolism could easily be indicted as the principal cause of the high prevalence of MS amongst medical personnel in Cameroon. Also over-indulgence in alcohol and excessive consumption of starchy staples could easily predispose to abdominal obesity, more especially if these excesses are not counter balanced by adequate and appropriate physical exercise regimen. Thus, result from this study show that there is a high risk of lifestyle-associated diseases within a group of people who are responsible for promoting health and healthy values and behaviours among the population.

That the NCEP/ATP III criteria (NCEP, 2002) and the IDF (2005) definition (Alberti et al., 2005) give different values for the MS prevalence rate is understandable, being mindful of different cut off values of the different components defining these two definitions. The WHO (1999) (Alberti and Zimmet, 1998) definition gave a prevalence rate of 0.00%, suggesting it is the least sensitive of the three definitions used. Identifying the lifestyle changes among the youth that could determine the increased tendency to develop risk factors for the diseases such as rural to urban migration and adoption of western habits (Rees et al., 2007) is a very important aspect in the prevention of the metabolic syndrome. This is because the hospital personnel are also victims of this westernization of habits especially diets. Our study reveals that only a minority of medical community are aware of MS as a clinical entity. Nurses and other paramedics appear to be unaware of the problem and this has also been reported by other investigators (Alam et al., 2011). Moreover, future interventions by health policy makers and public health officials ought to focus on the individuals at risk who have one or two risk factors in order to control any potential burden of the syndrome. In hospital based prevalence study involving 1974 patients undertaken by our team, it was observed that the MS prevalence rate for the general public was 8.4% which is not very different from the 7.5% obtained for hospital personnel, and this suggests that successful prevention campaigns against this syndrome must include all sectors of society.

We therefore recommend that the detection of risk factors for CVD among health personnel in Cameroon be included as part of a routine medical review. Such

interventions would be more expeditious among health personnel who have the advantage of immediate access to medical care. Programmes that promote healthy lifestyles among government employees, particularly in the health sector, are also highly desirable and should form part of government policy.

Conclusion

The present study shows that only a minority of medical community are aware of MS as a separate clinical entity. These findings indicate the need for evidence-based health promotion and disease prevention programs and more robust efforts directed towards the screening, diagnosis and management of MS and its components among Cameroonian medical personnel and the population at large.

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Full Length Research Paper

Evaluation of the results obtained from isokinetic muscle test in patients with primary fibromyalgia syndrome

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The aim of this study was to investigate whether the subjective muscle skeleton complaints of patients with fibromyalgia have an objective basis and the usability of muscle test results for diagnosis of fibromyalgia. 20 patients having primer fibromyalgia syndromes (PFS) who conforms to the criteria suggested by the American Rheumatism Association and a control group of 20 healthy people performed isokinetic muscle test over the right quadriceps and hamstring muscle group by Cybex 6000. In this study, maximum torque (MT), the ratio of maximum torque over body weight (MTWA), torque acceleration energy (TAE), total work (TW), set total work (STW), average power (AP) and endurance ratio (ER) were measured for muscle performance. A significant difference was found between the tests showing the muscle performance between the patients and the control group except the ER parameter. This difference was smaller in patients with fibromyalgia. As a result, it is decided that the objective low values in the muscle tests which are observed in patients with fibromyalgia are significant and isokinetic quantitative muscle test is a quite reliable method which can assist the doctor for the diagnosis of fibromyalgia. There exists a connection between the general fatigue and pain complaints of the patients with PFS and muscle deficiency. This muscle deficiency can be measured numerically by objective isokinetic methods. We argue that these measures should be utilized in the diagnosis and follow-up of patients.

Key words: Isokinetic testing, fibromyalgia, muscle.

INTRODUCTION

Primary Fibromyalgia Syndrome (PSF) is a non-inflammatory, painful musculoskeletal disease, accompanied by fatigue and many somatic complaints. It affects approximately 5% of the population, especially young women aged between 20 and 50 (Wolfe et al., 1995; Kuran et al., 1994). PFS is the most common reason of the disability claims (Bennet, 1993; Yunus, 2012). In this disease, which has important individual, social and economic outcomes, routine laboratory analyses and rheumatologic analyses are normal (Yunus and Masi, 1993; Ang et al., 2011; Alnigenis and Barland, 2001). In the cases of PFS, the results of the scintigraphic and electromyographic examinations are normal (Maquet et al., 2002; Hooten et al., 2012).

In all the patients with fibromyalgia, there are widespread pain and many tender points. In many patients, varying degrees of fatigue, morning stiffness, depression, non-relaxing sleep and post-activity pain exists (Thomas, 2011; Buskila, 2009; Alok et al., 2011; Ang and Wilke, 1999). In approximately one third of the patients, irritable bowel syndrome, headache, premenstrual syndrome, female urethral syndrome, numbness and tingling, sicca symptoms and Raynaud phenomenon are observed

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(Bennet, 1993; Tuna, 1994; Yunus and Masi, 1993). PFS is diagnosed by detecting the tender points based on the physical examination.

More than 20 parameters may be used during the isokinetic tests. Here, we will review the most commonly used parameters (Davies, 1992; Miskioğlu, 1995).

1. Torque: This is the tendency of a force to rotate an object around a rotational axis. Torque, which can be briefly defined as “rotational momentum”, is equal to the product of the force and distance.
2. Maximum Torque (MT): This is the maximum value for the torque that is obtained in all the points and in all the repetitions within the range of motion. This is the most commonly used parameter.
3. Maximum Torque to Body Weight Ratio (MTWA %): This is calculated by the device by multiplying maximum torque/body weight ratio by 100.
4. Torque Acceleration Energy (TAE): It is the energy spent within the first 1/8 second of the torque formation or, in other words, it is the total work produced.
5. Total work (TW): It is the total volume that remains under the torque curve at each repetition, regardless of the velocity, ROM or time.
6. Set Total Work (STW): It is expressed as joule.
7. Power: It is the work produced in one unit of time. It is expressed as Watt or Newton-meter/second. It is the total volume that remains under the torque curve at each repetition, regardless of the time.
8. Average Power (AP): Total work/time.
9. Endurance ratio (ER): It is the ratio of the number of repetitions that the patient does at the beginning and at the end of the exercise. It is the ratio of the work produced at the first 20% of the total repetitions to the work produced at the last 20% of the total repetitions.
10. Comparison of agonist/antagonist: It is the ratio of maximum torque of total work parameters. The result is expressed as percentage.

The aims of the isokinetic test include objective recording, athletic and industrial screening, test to build up a data bank, conversion of the objective data to numeric data, the determination of whether a person really has the disease, the detection of compensated cases or the cases with disability, the demonstration of the pathologic conditions using torque curves and the determination of the normal values.

In this study, we aimed to discuss the utility of the results obtained from isokinetic muscle test in the diagnosis of fibromyalgia.

MATERIALS AND METHODS

We enrolled to the study of 20 patients with primary fibromyalgia syndrome (PFS) according to 1990 criteria of the American College of Rheumatology and 20 healthy subjects with same demographics to form a control group. All patients had systemic examination and routine laboratory analyses. The patients with an additional systemic or local problem were excluded from the study. As the test was performed on the knee articulation, special attention was paid to select the patient without knee pain to include in the study. All patients were questioned for age, gender, body weight, life style and disease-related characteristics. The subjects who were doing more activity, including sport-intended jogging for half an hour per day, were considered as active, whereas others were considered as sedentary. We built our study group from the sedentary patients. Control group was built by ensuring the consistency with the patient group in terms of age, gender, weight and life style.

Strength analysis of the flexor and extensor muscles of the knee was performed using Cybex 6000 isokinetic dynamometer (1991 to 1993 Cybex 6000 Testing & Rehabilitation System; CYBEX Division of LUMEX, Inc., Ronkonkoma, New York). The device was calibrated before the testing. Before beginning the tests, the patients were comprehensively instructed about how and why the test would be performed. Before the test, the patients and the controls did exercise using bicycle ergometry for 15 min in order to warm up. The test was administered within an articular range of motion of 0 to 90°, by considering full extension of the knee articulation as the anatomical zero point. While trunk and hip stabilization was ensured using the trunk belt provided with the device, the articulation was stabilized using a Velcro band that was passed through the proximal of the knee, by keeping the trunk perpendicular to the floor and the hip articulations at 90° flexion. Transverse line that passes through the femoral condyles was accepted as the axis for the knee articulation and the axis of the dynamometer was set to this position. All tests were performed by the same operator. Similar auditory and visual stimuli were given.

In this study, the following parameters were used: Maximum torque (MT), Maximum torque to body weight ratio (MTWA), Torque acceleration energy (TAE), Total work (TW), Set total work (STW), Average power (AP), Endurance ratio (ER). Data were evaluated using “Statistica” software loaded on the computer. As the groups did not meet the parametric test requirements, non-parametric Mann-Whitney U test was used. Significance level was considered as $p < 0.05$.

RESULTS

This study was performed on a total of 40 people, including 20 patients with PFS and 20 normal healthy people. Each group included 19 women and 1 man. Demographics of the patient and control groups are shown in Table 1. As seen in the table, patient and control groups were very close to each other in terms of age, height and weight and there was no statistically significant difference ($P > 0.05$). Both groups were sedentary in terms of physical activity. Table 2 shows the answers that the patients gave to the questions that we asked through forms. Of these questions, seven concerned the clinical signs of the disease, one concerned the relation of these symptoms with the climate and one concerned whether they underwent a surgical operation.

In this study, we used seven parameters. We constructed a table for each parameter. In the tables, mean, standard deviation and “p values” of the patients and of the controls for each data are presented.

Table 1. The characteristics of patients and control group.

Parameter	Patient group	Control group
Male	1	1
Female	19	19
Age (Mean)	36 (17-47)	35.8 (17-48)
Height (cm)	157 (148-165)	162 (150-172)
Weight (kg)	64 (48-80)	67 (50-90)
Physical activity	Sedentary	Sedentary
Duration of disease (year)	3.3	-

Table 2. Clinical symptoms of patients.

Clinical symptom	No. of patients	%
Fatigue in the morning	15	75
Stiffness in the morning	16	80
Insomnia	16	80
Chronic headache	16	80
Irritable bowel	12	60
Relationship between climate	16	80
Numbness in extremities	16	80
Decreased libido	9	45
The history of operation	5	25

DISCUSSION

Majority of the patients present in the clinics of rheumatology had fibromyalgia. When these patients were evaluated by several functional disability indexes, it was seen that the diseases restricted the activity of the person as much as rheumatoid arthritis. As seen in Table 3, the incidence rates of the clinical symptoms exhibited by the patients enrolled to our study are consistent with previous studies. In the patients that we examined in our study, 20% had a history of surgical operation, which was a rate that should not be ignored. The patients with fibromyalgia complained of widespread musculoskeletal pains. However, the muscular biopsies performed for this purpose did not reveal a specific finding belonging to the disease, except small non-specific changes (Tuna, 1994; Goldenberg, 2009). There are limited numbers of studies to investigate blood test in the patients with fibromyalgia (Ang et al., 2011). In these studies, only one or two parameters were used. In our study, we also used some other parameters that showed muscular performance.

As done in other studies, we chose quadriceps and hamstring muscle groups which are the second biggest muscle of the body, and right side, which is the dominant Side, because during direct or indirect muscular pathologies, the likelihood that the first symptoms appear in these muscles is relatively higher.

Muscular strength examination (manual muscle test), which is done within routine physical examination, is a qualitative method, which provides quite subjective data. Additionally, it may result to evaluation errors depending on the muscular performance and experience of the person who administers the test. Especially in mildly affected cases, it may be difficult to reveal a mild motor deficit. Similarly, some inadequacies may be observed in the detection of minor changes that occurred during the follow-up of the patient (Karataş, 1994; Byl et al., 1991).

Cybex 6000 isokinetic dynamometer that we used in our study allowed us to perform a completely quantitative and extremely reliable muscular strength test. This system provides the possibility to individually examining the isolated muscles or muscle groups or to investigate them in terms of reciprocal muscular activities. It is easy to monitor the progress and to evaluate the data. With these features, it may be suggested that the method used is among the most reliable quantitative methods that have been used to date in the literature (Gross et al., 1991; Molczyk et al., 1991; Kannus, 1994).

For the functional evaluation of the muscles surrounding the knee, different isokinetic test protocols were used in several studies. Several parameters were investigated by using different angular velocities. In our study, we used MT and MTWA parameters to determine muscular strength because MT was the most commonly used and best-studied parameter in the isokinetic strength tests to date (Miskioğlu, 1995). In the literature, for MTWA parameters that we used in addition to MT, it was stated that MTWA provided a different point of view in the interpretation of the test results. Occasionally, although bilateral comparisons or a unilateral rate of the person is normal, the relation of torque by body weight may be different (Li et al., 1996; Norregaard et al., 1994). As body weight varies, it is more appropriate to use MTWA to perform interpersonal muscular performance comparisons.

While isokinetic muscular strength negatively regresses with advanced age, it increases proportionally to body area and body surface area (Avin and Law, 2011). When isokinetic parameters are globally considered, the observation that angular velocity increases with decreasing MT and MTWA values in all groups is impressive. The aforementioned feature applies to both extensor and flexor muscles. Again, the results obtained from all the tests performed in this study were parallel to this. This relationship is consistent with many isokinetic investigations conducted on the muscles that surrounded the knee which have been cited in literature (Jacobsen and Danneskiold-Samsoe, 1992; Maquet et al., 2002; Norregaard et al., 1994; Hooten et al., 2012).

Another fact related to known isokinetics is that MT will be formed later in ROM (range of motion) with increasing angular velocity. This is especially important when a study is conducted with the muscle groups with strength loss because, as MT will occur at a late stage, when higher

Table 3. The common symptoms of PFS.

Parameter	Yunus (33)	Goldenberg (32)	Uslu (31)	Our study
Total number	113	118	30	20
Average age	40	43	38	36
Female (%)	94	87	83.3	95
Disease duration (year)	6.9	5	-	3.3
Morning stiffness (%)	76	76	-	80
Fatigue (%)	85	92	80	85
Sleep disturbances (%)	62	80	67	80
Feeling of swelling (%)	40	50	63	80
Irritable bowel (%)	41	53	37	60
Headache (%)	58	55	60	80
Decreased libido (%)	-	-	-	45
Relation of climate (%)	-	-	-	80
Previous operation (%)	-	-	-	20
Raynoud phenomenia (%)	12	-	-	-

higher velocities are used, optimal articulation position for MT will be passed over and the real muscular performance of the patient will not be determined (Osternig, 1986; Lord et al., 1992; Kannus and Beynnon, 1998). Therefore, the reliability of the test decreases at high velocities such as 300°/sn. On the other hand, low velocity of 60°/sn and intermediate velocity of 180°/sn are not problematic in terms of reliability. We can tell it by observing the isokinetic graphics.

Lower velocities place higher loads on the articulation compared to higher velocities. In 1970s, Cybex proposed 30°/sn to perform a test on the knee. Today, it proposes 60°/sn, because 30°/sn is not a natural velocity and increases the load placed on the articulation and inhibits the strength. Additionally, the test conducted at 30°/sn does not provide any additional information upon the test conducted at 60°/sn (Sole et al., 2007). The velocity should be selected by taking into account the patient characteristics and the goal of the therapy. Many investigators reported high reliability of neuromuscular parameters such as work and power as well as concentric maximum torque (Steiner et al., 1993; Adsuar et al., 2011). In the study performed by Barbee and Landis (1984), the investigators reported that MT, work and power values resulting from knee flexor and extensor muscles could be reliably measured in the normal subjects using Cybex II device, but TAE values were less reliable.

Özaras et al. (1995) performed isokinetic test for right and left knee extensor and flexor at 60°/sn and 180°/sn in 15 female patients with primary fibromyalgia and they could not find a statistically significant difference in terms of maximum torque values. In our opinion, this result demonstrated that there was no temporary or unilateral muscular involvement in the patients with fibromyalgia. Jacobsen and Danneskiold (1992) conducted a study on and Brodie, 1989; Holmes and Alderink, 1984).

In the study performed by Jacobsen et al. (1991), mean duration of disease was reported to be 11.5 years. When the angular velocity of 60°/sn that led to more load on the articulation and to more strain of the muscle, along with the duration of the disease was taken as basis for the endurance test, it would not be surprising that the patients with widespread musculoskeletal pain would leave the test during the first repetitions. When we evaluated the total work and average power values in our study, we saw that these values were very low in the patients (Tables 4 and 5). This demonstrated that in the real life, despite the inadequate muscular performance of the patients, because of the deficiency of the motivation required for the maximum voluntary muscle contraction, the patients began the test with the contractions that produced less work and they were less tired at the end of the test when they showed to have produced nearly the same work or more work compared to controls. In other words, here, we may see the disadvantage in question for the endurance test. In another saying, the patients have the problem of compliance to motivation. In this regard, we remember other literature studies that mentioned the central effect in the patients with fibromyalgia, because these results supported these studies.

Jacobsen et al. (1991) measured combined isokinetic and isometric muscle strength in the patients with fibromyalgia using transdermal electric muscle stimulation and they revealed that submaximal force was applied during the maximum voluntary muscle contraction of the patients. In the study performed by Margerata et al. (1994), voluntary muscle contraction was lower in the patients with fibromyalgia compared to controls. Again, submaximal values were found to be lower with the use

Table 4. The comparison of the knee flexor and extensor muscles isokinetic TW value at different angular velocities in the patient and the control group.

TW	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	42.75	13.41	69.2	18.29	7E-06
	180	31.9	9.73	49	14.67	0.00015
Extensor	60	61.7	15.5	93.1	19.9	3E-06
	180	39	12.1	59.7	13.3	3.1E-05

Table 5. The comparison of the knee flexor and extensor muscles isokinetic AP value at different angular velocities in the patient and the control group.

AP	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	27.35	8.8	44.7	11.8	9E-06
	180	57.45	17.3	85.55	25.6	0.00048
Extensor	60	39.4	8.8	60.4	13.2	3E-06
	180	70.6	23.5	111.7	25.9	3.3E-05

of superimposed electric stimulation. They suggested that decreased voluntary maximum muscle performance might result from an impairment of control mechanisms at supraspinal level. In our opinion, there is another study that would support this insight. Johnson (1982) measured dynamic force and endurance in the left quadriceps of 15 subjects aged between 20 to 29 and 15 subjects aged between 50 to 80 using Cybex II isokinetic dynamometer, and they showed that the force was decreased in the elderly, despite the endurance that remained constant. Probably, the elderly subjects could continue to the test because they made a submaximal effort.

In our literature search, we could not detect other parameters that showed muscular performance in the patients with fibromyalgia. The results about other parameters that we used in our study are summarized as below. In this study, isokinetic MTWA value, TAE value and STW value, at different angular velocities were significantly lower in the patient group in both knee extensor and flexor muscles at both 60 and 180° (Tables 7, 8, 9 and 10). This finding showed that fast muscular performance of the patients was weak. Total work (TW) and average power (AP) values were significantly lower in the patient group in both extensor and flexor muscles at both 60 and 180°. These latter parameters are somewhat the complements and providers of the other parameters. The results that we obtained from all the parameters that we used in our study were integrated and consistent. 15 patients with primary fibromyalgia and 15 healthy people. In these people, the strength of the knee extensors was isometrically and isokinetically measured using Cybex 2 dynamometer and as a result, muscular strength was found to be significantly lower in the patient group. The same investigators found that the isokinetic measurement was more reliable than isometric measurement because it provided more detailed information.

Norregaard et al. (1994) performed a study on 20 female patients with primary fibromyalgia where they found a significant decrease in the muscular strength. Therefore, they thought that exercise had an important place in the rehabilitation of these patients. Margaretta et al. (1994) conducted a study on 25 patients with primary fibromyalgia and on 22 healthy people and they found a marked decrease in the maximum voluntary muscle contraction of the patients. In our study, the results that we found for MT and MTWA indicating muscle strength showed a parallelism with the above-mentioned studies.

Jacobsen et al. (1991) conducted a comparative study to compare the muscle endurance between the patients with fibromyalgia and the patients with chronic myofacial pain. In this study, the last two knee extensions in which baseline contraction-related work value obtained at an angular velocity of 60°/sn using isokinetic dynamometer came up to 70% or below and the number of repetitions was used to determine the endurance. In addition, it was statistically demonstrated that the strength was decreased in the patients with fibromyalgia.

Table 6. The comparison of the knee flexor and extensor muscles isokinetic ER value at different angular velocities in the patient and the control group.

ER	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	180	92.8	18.7	88.7	13.8	0.54228
Extensor	180	87	18.9	79	12.2	0.12257

Table 7. The comparison of the knee flexor and extensor muscles isokinetic MT value at different angular velocities in the patient and the control group.

MT	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	39	10.7	60.6	14.1	0.000009
	180	31.6	8	43.1	11.2	0.000550
Extensor	60	68.5	14.5	103.1	22.3	0.000001
	180	40.5	12.3	60.4	12.3	0.000039

Table 8. The comparison of the knee flexor and extensor muscles isokinetic MTWA value at different angular velocities in the patient and the control group.

MTWA	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	64.5	20.3	90	24.7	0.0015
	180	50.2	12	63.6	17.8	0.0246
Extensor	60	110.5	28.7	152.3	34.6	0.0004
	180	64.1	17.6	88.5	16.6	0.0001

Table 9. The comparison of the knee flexor and extensor muscles isokinetic TAE value at different angular velocities in the patient and the control group.

TAE	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	2	0.6	3.8	1.7	0.000036
	180	8.8	2.1	12.7	3.6	0.000259
Extensor	60	2.8	0.8	5.8	2.6	0.000005
	180	10.3	2.9	16.7	4.6	0.000015

Norregaard et al. (1994) performed an endurance test in 20 female patients with fibromyalgia and found a slightly low endurance. The patients continued to the test until being exhausted or up to a maximum of 40 min, with 4 min contraction with half of the real muscle strengths and 6 s resting. Mean endurance time was found to be 22 min in the patient group and 29 min in the control group.

In our study, we measured the muscle endurance in the patients to whom we applied the test by asking them to do 20 repetitions at 180°/sn. We compared the work that occurred during the last 20% of the repetitions with the wok that occurred during the first 20% of the repetitions. We expressed the difference as percentage. We obtained a result that could initially seem inconsistent with the aforementioned studies, but in reality we obtained a result that was consistent with above mentioned studies by one aspect and that opened new horizons. Although there was no statistical significance, we obtained a higher rate of endurance in the patient group (Table 6). Traditionally recommended original endurance test is

Table 10. The comparison of the knee flexor and extensor muscles isokinetic STW value at different angular velocities in the patient and the control group.

STW	Angular velocity (°/sn)	Patient group		Control group		P
		Average	SS	Average	SS	
Flexor	60	192.1	70.1	315.1	86	0.000013
	180	535.2	164.5	798.1	254.9	0.000189
Extensor	60	262.5	77.6	42.4	95.9	0.000005
	180	625.95	202.43	929.25	209.8	0.000074

performed in a muscle group at the velocities of 180 or 240°/sn. Test is terminated upon a decrease of strength by 50%. However, as a disadvantage, the patient should be motivated during all testing period to obtain a maximum effort. Testing data should be supported with the values of total work and average power (Baltzopoulos

Conclusion

Consequently, it was concluded that objectively lower values observed in the muscle tests of the patients with fibromyalgia were significant and that isokinetic quantitative muscle test was an extremely reliable method that is helpful for the doctor to diagnose the fibromyalgia. General fatigue and pain complaints which are subjectively felt by the patients with primary fibromyalgia, are associated with muscular weakness. This muscular weakness may be numerically measured using objective isokinetic methods. We believe that these measurements will be useful in the diagnosis and in the monitorization of the patients. Decreased muscular performance observed in the patients may result from an impairment of the control mechanism at supraspinal level or may have a peripheral origin, whether related to above-mentioned impairment or not. Further studies should be conducted to elucidate this issue.

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Full Length Research Paper

Effect of cardiopulmonary physiotherapy on lung parameters in mechanically ventilated neonates

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Studies done in the past on cardiopulmonary physiotherapy in neonates, have not fully laid enough evidence, and several limitations have been quoted. The main purpose of this study was to evaluate the effect of chest physiotherapy, including suctioning on lung dynamics and lobar atelectasis. The secondary objectives were to explore sessions required to resolve collapse and the use of a detailed and replicable protocol of chest physiotherapy for ventilated neonates. Single group non-randomized blinded study design was used. Consecutive 42 mechanically ventilated neonates, consisting of 16 male and 26 female participants from a tertiary care hospital, with neonatal intensive care unit, was used for this study. Eleven babies were premature with 30 ± 3 weeks of gestational age whereas other babies had age of 15 ± 7 days after full term delivery. Techniques of cardiopulmonary physiotherapy, including humidification, positioning, postural drainage, percussion, vibration and endotracheal suctioning were applied. Dynamic compliance, inspiratory and expiratory resistance, reinflation of collapsed lung on chest x-ray were observed. The results found were statistically significant ($p < 0.0001$) for improvement in lung compliance, reduction in inspiratory and expiratory resistances, along with re-expansion of collapsed lobes. A carefully laid protocol of cardiopulmonary physiotherapy, individualized and when administered by an experienced and well trained cardiopulmonary physiotherapist, in association with multidisciplinary approach shows improvement in lung dynamics of ventilated neonates.

Key words: Neonates, mechanical ventilation, cardiopulmonary physiotherapy.

INTRODUCTION

Delivery of a baby from the mother's womb into the world is the most catastrophic event in a child's life. All babies compulsorily undergo the trauma of birth where there is a complex transition of placenta respiration to gas exchange in the lungs (Hough, 2001). Neonates, with compromised cardiorespiratory functions due to any reason, face a world where they have limited defenses in terms of respiration, kidney function or temperature control (Prasad and Hussey, 1995). Neonatal chest physiotherapy has become a routine method of care in neonatal intensive care units in the Western world while the same is less common in India, probably due to shortage of cardiopulmonary physiotherapy training in pediatrics and neonates (Bruno Demont and Claude Vincon, 2007).

Physiotherapy is generally sought when there is excess secretion, poor gas exchange, and increased work of breathing or radiologic evidence of atelectasis. Chest physiotherapy reference to treat post-extubation atelectasis is more common than treatment while babies are on mechanical ventilation. In our setting, chest physiotherapy for babies on ventilators is common, especially to treat lobar collapse. There are different techniques of cardiopulmonary physiotherapy (CPT) including humidification, positioning, postural drainage, percussion, vibration and endotracheal suctioning (Tudehope and

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Table 1. Demographic characteristics of subjects (n = 42).

Parameter	Mean ± SD
Age (days after delivery)	15±7
Age of 11 preterm babies (gestational age in weeks)	30±3
Gender (M/F)	16:26
Weight (g)	1577.8±331.7
ET size (mm internal diameter)	3.5±0.5
FiO_2 (%)	50±21
Respiratory rate (breaths per minute)	46±11
Peak inspiratory pressure (cmH_2O)	25±7.6
PEEP (cmH_2O)	5.0±2.8
Lobes involved (1:2 lobes)	29:13

Table 2. Primary medical diagnosis of subjects (n = 42).

Diagnosis	Subject (n = 42)
Respiratory distress syndrome	15
Transient tachypnea of newborn	04
Meconium aspiration	07
Pneumonia	11
Sepsis	02
seizure	03

Bagley, 1980; Oberwaldner, 2000).

Studies done in the past over CPT in neonates have not fully laid enough evidence, and several limitations have been quoted. A Cochrane review aimed to assess the effects of active CPT techniques, such as percussion and vibration, followed by suction compared with suction alone on the respiratory system in infants receiving mechanical ventilation. The results of this review did not provide sufficient evidence on which clinical practice can be based (Hough et al., 2008).

Another Cochrane review aimed to assess the effects of different positioning of newborn infants receiving mechanical ventilation on short term respiratory outcomes and complications of prematurity. The prone position was found to slightly improve the oxygenation in neonates undergoing mechanical ventilation. However, they found no evidence concerning whether particular body positions of the neonate during mechanical ventilation are effective in producing sustained and clinically relevant improvements (Balaguer et al., 2006).

The main purpose of this study was to evaluate the effect of chest physiotherapy, including suctioning on lung dynamics and lobar atelectasis. This study also tried to explore sessions required to resolve collapse, and lay down a detailed and replicable protocol of chest physiotherapy for ventilated neonates.

MATERIALS AND METHODS

This study was approved by the Institution's Ethic Committee. All mechanically ventilated neonates who were one month old after delivery were included in the study. Demographic characteristics of all subjects are shown in Table 1. A total of 42 subjects were recruited over a year. Out of 42 babies, 11 were pre-term. Age, gender, weight, primary medical condition, oxygenation and ventilation requirement, along with Positive end-expiratory pressure (PEEP) and PIP were recorded.

All the babies were followed up from the first day of ventilation. Prior to suctioning, all subjects were humidified with the help of an electronic nebulizer by bronchodialator. The babies were placed on both sides, lying for 10 min, and percussion was performed with the help of a mask. Vibrations with three fingers in tented position were applied to mobilize secretions for all the babies. Standard procedure was followed for each technique (Prasad and Hussey, 1995).

The suctioning procedure was performed as follows: (1) subjects were pre-oxygenated with 100% inspired oxygen for one minute prior to suctioning; (2) subjects were disconnected from the ventilator; (3) a suction catheter was passed down the endotracheal tube to beyond the tube tip while kinking the catheter; (4) on reaching the tip, continuous suction was applied, and the catheter was withdrawn while rotating slightly; (5) the subjects were then immediately hyperinflated with pediatric AMBU of 500 ml volume, while inflating only half the volume which was connected to 4 L/min of oxygen supply. If there was noted failure of desaturation with AMBU, the baby was reconnected to the ventilator circuit. Any adverse events were documented.

A catheter size of 6 fg was used, which was ideal according to endotracheal tube size. The suction apparatus was set to deliver a negative pressure of -60 to -80 mmHg. The suction catheter was in the endotracheal tube for <15 s.

Upon completion of suctioning, babies were reoxygenated with 100% FiO_2 for 30 s, and then the FiO_2 was immediately changed to presuction settings unless desaturation occurred, in which case, FiO_2 was gradually turned down as SpO_2 improved. Chest physiotherapy sessions, including suctioning, were provided by the first and the second authors. Recordings of outcomes were done for two sessions in morning and afternoon, on two consecutive days. Outcomes were recorded before and after each session at the 10th, 30th and 45th min. Dynamic compliance (DyC), inspiratory resistance, and expiratory resistance were major outcomes to understand the effect of intervention over lung dynamics. A chest X-ray was taken after an hour of each session to confirm resolution of lobar collapse.

Data analysis

Data was analyzed by SPSS (version 16.0; SPSSinc. Chicago, Ill USA). A blinded data analysis was used. ANOVA with repeated measures was used to analyze the changes in outcome variables across the sessions. Adjustments for multiple comparisons were done by Boneferroni test.

RESULTS

A total of 42 neonates were recruited for this study out of which 11 babies were preterm. Baseline characteristics of all neonates, including age, gender, weight, ET size, FiO_2, respiratory rate (RR), positive end expiratory pressure (PEEP), and lobar collapse are shown in Table 1. All

Table 3. Changes in outcome variables across the sessions (n = 42).

Variable	Day 1, Session 1 (min)				Day 1, Session 2 (min)				p
	Pre PT	Post (10)	Post (30)	Post (45)	Pre PT	Post (10)	Post (30)	Post (45)	
Dynamic compliance	31.3 ±5.7	32.0±5.5	32.3±5.6	32.1±5.5	31.4±5.6	31.7±5.4	32.1±5.5	32.5±5.2	0.003
Inspiratory resistance	58.0±7.8	50.5±8.1	47.1±6.3	51.8±8.8	59.8±5.2	54.9±6.6	52.1±6.7	48.4±8.1	≤0.0001
Expiratory resistance	87.0±5.8	82.6±7.4	82.7±6.9	83.9±6.1	88.2±8.5	84.2±7.9	84.9±5.1	85.4±5.8	≤0.0001
	Day 2, Session 3 (min)				**Day 2, Session 4 (min)**				
Dynamic compliance	31.8±5.4	32.0±5.5	32.5±5.7	33.6±5.8	33.0±6.4	34.0±7.8	34.7±9.3	37.5±11.9	≤0.0001
Inspiratory resistance	58.7±8.5	55.7±6.4	50.3±6.7	49.3±8.4	58.0±8.2	58.0±7.4	58.0±7.6	58.0±7.1	≤0.0001
Expiratory resistance	88.1±4.9	79.9±9.1	82.8±8.6	80.6±10.1	83.0±10.5	80.2±8.4	81.6±9.5	78.9±11.2	≤0.0001

1. All the babies had a primary medical diagnosis which necessitated use of mechanical ventilation, and details of diagnoses is shown in Table 2. When dynamic compliance was recorded, pre and post CPT at 10th, 30th and 45th min yielded a significant difference in each session; however differences were more after the 3rd and 4th sessions on the second day ($p \leq 0.0001$). Inspiratory and expiratory resistances showed highly significant reduction after each session, and these differences are statistically ($p \leq 0.0001$) as well as clinically significant. The mean changes with standard deviations after each session with p values are mentioned in Table 3. Sessions required to show resolution of lobar collapse on chest x-ray (CXR) ranged from 2 to 3, and mean with standard deviation was 2.6 ± 0.78.

DISCUSSION

This study recruited 42 consecutive neonates who were mechanically ventilated due to primary medical diagnoses as shown in Table 2. Our study tested the efficacy of a full treatment protocol in neonates for the first time. Dynamic compliance improved from pre to post chest physiotherapy in all sessions. However, dynamic compliance improved more after second session on second day. This could be attributed to reinflation of collapsed lobes of the lungs and secretion clearance.

Inspiratory resistance reduced from pre to post in all sessions, which was clinically significant. There was no reduction or increase in inspiratory resistance after session 2 of the second day. This finding requires further investigation while one probable reason could be minimum stable resistance during the last session. Expiratory resistance also decreased from pre to post chest physiotherapy after all sessions on both days. This change was statistically and clinically meaningful. These positive changes could be due to secretion clearance and relieved bronchospasm which stabilizes the chest and improves compliance as well.

A study by Morrow et al. (2006) reported a reduction in compliance and increase in resistances post suction which could be attributed to the fact that readings were taken immediately upon post suction. Report on whether values stabilized or not over a long period of time was not done. We have taken readings at 10th, 30th and 45th min of post CPT sessions to see changes in values over a period. It is noteworthy that values showed more stability after 10 min. Another study reported an improvement in lung compliance and reductions in resistances after CPT and data was recorded past 10, 40 and 70 min. Findings of this study are in parallel with our study (Mara Lisiane et al., 2009).

In another study, patients were randomized into one of three treatment groups: Group 1 (suctioned only); Group 2 (positioned and suctioned); and Group 3 (positioned, manually hyperinflated and suctioned). Baseline and 10, 30 and 60 min post-treatment data were recorded for dynamic pulmonary compliance, arterial blood gases and haemodynamic variables. Derecruitment was an important finding reported by authors (Barker and Adams, 2002). Sessions required for reinflation of collapsed lung on chest X-ray was three, however this change was dependent on the number of lobes involved. More than one lobe involvement took more sessions for re-expansion than single lobe involvement.

Some studies reported adverse effects of CPT like hypoxemia, bruising, rib fractures and intracranial hemorrhage due to which efficacy of

CPT has been questioned. In our study, these adverse events did not occur. We believe that Neonatal intensive care unit (NICU) is a unique environment and requires the best skills and expertise before handling the neonate.

Three trials involving 106 infants were included in a Cochrane systematic review, which showed conflicting results (Hough et al., 2008). In one trial (n = 20), CPT was not better than standard care in clearing secretions. In the review, author has defined active CPT as vibration or percussion, with or without the use of devices such as face masks and electric vibrators, followed by suction, compared with standard care (that is suction with or without positioning). No increase in the risk of intraventricular haemorrhage was noted (Raval et al., 1987). The other trial (n = 30) showed that the use of percussion or 'cupping' resulted in an increased incidence of hypoxaemia (RR 0.53; 95% CI, 0.28 to 0.99) and increased oxygen requirements (MD -9.68; 95% CI -14.16 to -5.20) when compared with contact heel percussion. There was insufficient information to adequately assess important short and longer-term outcomes, including adverse effects (Peters, 1983). In another trial (n = 56), it showed that non-resolved atelectasis was reduced in more neonates receiving the lung squeezing technique (LST) when compared to postural drainage, percussion and vibration (RR 0.25; 95% CI, 0.11 to 0.57). No difference in secretion clearance or in the rate of intra-ventricular haemorrhage or periventricular leucomalacia was demonstrated (Wong and Fok, 2006).

Authors of the same Cochrane review have recommended that further well-designed trials are required to assess the risks and benefits of CPT in the treatment of respiratory diseases in ventilated neonates. Future trials should be adequately powered to address clinically important outcomes, particularly for the high risk population of infants < 30 weeks gestation. Clinically important outcomes which should be assessed include duration of ventilation, duration of oxygen therapy, length of hospital stay, and presence of intracranial lesions. Shorter-term outcomes such as resolution of atelectasis, oxygenation, and other lung function variables such as ventilation distribution should also be included. Costs also need to be considered. Some of the important clinical and economic outcomes that remain unmeasured by the current research are likely to require a very large sample size, therefore, a large multicentre trial would be recommended. We could not randomize our study but we have taken few recommended outcomes as our study outcomes (Hough et al., 2008).

In a study done by the same author, lung mechanics were recorded for five minutes before and five minutes after a standardized suctioning procedure in 78 patients intubated with endotracheal tubes (≤ 4.0 mm internal diameter). There was a significant overall decrease in dynamic compliance ($p < 0.001$) and mechanical expired tidal volume ($p = 0.03$) following suctioning, with no change in the percentage endotracheal tube leak ($p = 0.41$). The change in dynamic compliance was directly related to both endotracheal tube and catheter sizes. This study demonstrated that endotracheal suctioning frequently caused an immediate drop in dynamic compliance and expired tidal volume in ventilated children with variable lung pathology, intubated with small endotracheal tubes, probably indicating loss of lung volume caused by the suctioning procedure (Morrow et al., 2006). Our study showed no reduction in dynamic compliance while the changes in inspiratory and expiratory resistances were significant.

A review was done by Morrow and Argent (2008) to provide evidence-based review of pediatric endotracheal suctioning, its effects, indications, and clinical practice. One hundred and eighteen references were included in the final review. Despite the widespread use of endotracheal suctioning, very little high-level evidence was found. Authors concluded that suctioning should be performed when obstructive secretions are present, rather than routinely. Authors further recommended that routine saline instillation before suctioning should not be performed. In addition, recruitment maneuvers performed after suctioning have not been shown to be useful as a standard practice. They further recommended that controlled clinical studies are needed to develop evidence-based protocols for endotracheal suctioning of infants and children, and to examine the impact of different suctioning techniques on the duration of ventilatory support, incidence of nosocomial infection, and length of pediatric intensive care unit and hospital stay.

A previous study has reported that chest and motor physiotherapy improved cardiovascular parameters in respiratory distress syndrome newborns (Abreu et al., 2011a). Torigoshi et al. (2011) recommended the implementation of a specialized newborn health accompaniment after neonatal ICU discharge for proper and positive outcomes regarding their future growth and development, is of uttermost importance for proper and positive outcomes regarding newborns future growth and development in Brazil. A study reported that chest and motor physiotherapy acutely improves heart rate (HR), RR, symptom association probability (SAP), minute-to-minute mean arterial pressure (MAP) and SO_2% in newborns with Acute respiratory distress syndrome (ARDS), where comparisons of outcomes were made between six sessions on same day (Abreu et al., 2011b). Chest physiotherapy, along with motor physiotherapy treatment, acutely improved SO_2%, HR and RR in premature Peri-Intra-Ventricular Hemorrhage (PIVH) newborns. Authors recommended performing chest and motor physiotherapy in neonatal critically ill newborns (Abreu et al., 2011c).

Our study has examined few aspects of the recommendations by the authors. An important fact lying in neonatal study is who performs the intervention, and therapist's experience of working with neonates. A lot of misoccurrence can be avoided by proper handling and adequate monitoring while treating the baby. A rescue

must be brought in at any point of intervention if there is consistent fall in SpO_2 or change in Electrocardiography (ECG) or other vitals. A multidisciplinary team for neonates in NICU comprises of supervising Neo-nathologist/ pediatrician, Cardiopulmonary physiotherapist therapist, Child psychologist, NICU nurses, and parents of the baby. Regular discussions about the baby among the team can fetch better results over the outcome of the baby.

There are several limitations of this study. This study is non-randomized with no control group, and sample size was not calculated. We recommend future researches based on randomized control trials, and also to understand whether chest physiotherapy during ventilation period minimizes the risk of post-extubation atelectasis. However, this study tried to explore the effects of chest physiotherapy in neonates, which is still a less researched area. This research also tried to explore important parameters which determine recovery of neonates with a systematic CPT approach.

Conclusion

Chest physiotherapy in ventilated neonates is a popular treatment choice but there is lack of evidence due to shortage of studies in this area. A well designed chest physiotherapy protocol and multidisciplinary approach may help ventilated neonates in improvement of lung dynamics and atelectasis.

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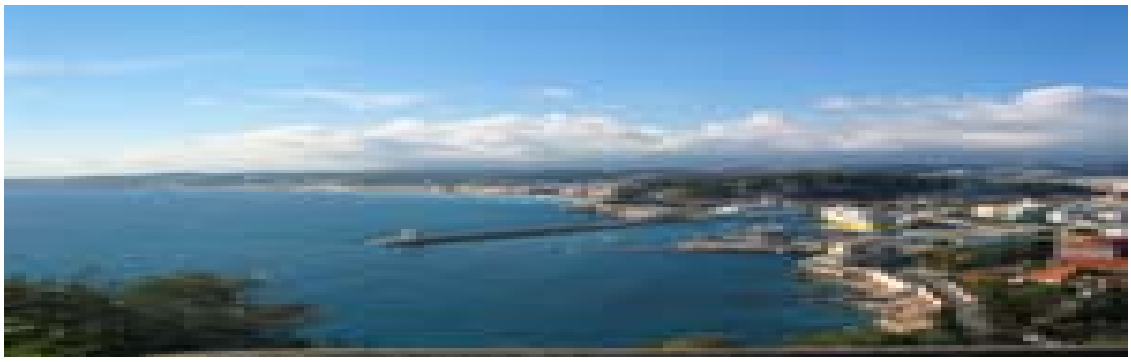

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