Medical Students Need a Global Perspective

It is not possible to curtail medical training to a unique population thought to define the Irish nation, just as it is not ethical to favour healthcare to some and not others because of a lack of awareness and ability, and feelings of responsibility. We are responsible because we are tied to global issues. We are responsible because, for want or not, Irish healthcare is increasingly absorbed by globalisation. The Irish Ethos, and the national issues of Ethics, Economics, and Environment, each impose an influence on the nation's care of the health of its citizens, and each are fated to be influenced and altered under accelerating globalisation. Future Irish medical graduates need and ought to demand a broad medical foundation to cope with the changing climate and to enable them an involvement in global healthcare issues as Ireland expands its presence internationally.

Trade, information exchange, and human migration define nations and limit the impact of borders. Increasing interconnectedness over the past decade has brought many beautiful new faces to Ireland and has pluralized major centres such as Dublin. Patient populations are less homogenous than a generation ago, and health professionals in this country are increasingly encountering diseases, choosing management plans, and facing outcomes that would have been uncommon or even remote in the past. Population statistics for common illnesses are slowly changing to parallel this new demography, and rare diseases such as sickle cell anaemia, which are associated with certain groups more dramatically than others, are on the rise.

The increasing disintegration of national boundaries complicates procedures aimed at preventing the spread of illnesses, particularly the spread of infections like tuberculosis: a disease of serious concern to the Irish health system. It also mandates that Irish clinicians be alert to the social, political and economic issues of foreign nations. The reason is simple: Instability in one part of the world creates an unstable situation for the health of the whole. The migration of people across borders increases as regions of the world become volatile due to war or economic depravity. The compassion of the Irish people, and the growing Irish prosperity has led to Ireland increasingly being the end destination. Consequently Irish clinicians are encountering refugees and asylum seekers and their specific physical and psychiatric problems more often.

Clearly Ireland's welfare is tied through global interdependence to the instability of other countries. Therefore over the last decade, out of both a genuine expression of concern, increased prosperity, and a need to invest in the security of its own healthcare and more, Ireland has engaged with several disadvantaged countries at many levels. Irish clinicians may wish to participate in these programs for reasons of gaining personal satisfaction, appreciating diversity, challenging prejudices, and/or expanding skills and knowledge. They will need a sound understanding of the destination's health problems, epidemiology, medical practices, infrastructure, social structure, and political climate. To gain an early start, or indeed simply for the fact that doctors are seen as experts on all subjects related to health, it is necessary that future clinicians learn of the prevalent illnesses seen globally and to appreciate genetic, cultural and environmental differences amongst populations. To those clinicians who feel it is not necessary, then let them consider that medical ethics has always held that medicine has a duty to help those in need, no matter where they may be from and as can be seen from the articles throughout the journal students have benefited greatly from experiencing different cultures throughout the world.

The future mandates that culturally sensitive and tolerant physicians graduate from the nation's medical colleges. Medical students require an undergraduate training that exposes them to the traditions, lifestyle, and the truths of the economic and social realities of different nations. They must be trained to be compassionate and to empathise with peoples of all races and customs, as well as be trained technically to recognise and diagnose the common spectrum of diseases seen globally that are now presenting to hospitals in Ireland. It is not wise to teach healthcare issues solely from a national perspective, as it is not wise to remain ignorant of

Penetrating Abdominal Trauma

Jarrod Wall

INTRODUCTION

Penetrating abdominal trauma is not uncommon and is usually associated with stab wounds, impalement and less commonly bullet wounds or explosions. The mortality associated with penetrating trauma can be low if cases are managed promptly and appropriately.

MANAGEMENT

The history and physical examination give a very good indication of the presence of significant visceral injury. Initially, management should include simultaneous evaluation and treatment, and begins with ABC's.[1] The key factor in deciding the immediate management of a case of penetrating abdominal trauma is the patient's haemodynamic stability.[1] Regardless of injury type, if the patient is haemodynamically unstable, they should be given aggressive fluid resuscitation, intubated and taken to theatre. Haemodynamically stable patients can be managed more selectively.[2]

MECHANISM OF INJURY

Knife Wounds

Stab wounds are more common than bullet wounds and are generally less lethal, unless they enter the retroperitoneal space to injure the great vessels or pancreas. For many years, a laparotomy was deemed mandatory following any form of penetrating abdominal trauma. However recently, trauma centres have been using a more selective approach, particularly in management of stab wounds and even gunshot injuries.[3] This is partly due to the increased frequency of and therefore experience with penetrating trauma. It is also related to the greater accessibility and quality of imaging techniques.[4] It has been found that 66% of stabbings enter the peritoneal cavity but less than 50% result in a visceral injury necessitating operative repair.[1] Therefore adoption of a policy of 'expectant observation' can be utilised. That is, observe the patient carefully and regularly for signs of internal haemorrhage or peritonitis, and if present, laparotomy should be performed immediately.[5]

Penetrating flank wounds are associated with injury to the colon, duodenum, kidney and major vascular structures. Therefore life-threatening injuries may exist despite haemodynamic stability and negative diagnostic peritoneal lavage (DPL, below). In this situation most surgeons have a low threshold for early abdominal exploration, particularly if the injury is thought to encroach on significant retroperitoneal structures as indicated by radiological imaging.[1]

Bullet Wounds

Injuries due to firearms are related to the ballistics of the weapon, the trajectory of the missile and the tissues or organs involved. The wounding potential of bullets is determined largely by its kinetic energy (KE) on impact ($KE = mass \times velocity^2$). Bullet wounds can be divided into low velocity (civilian injuries) and high velocity (military weapons). Low velocity weapons mostly produce injury by direct crush and tearing mechanisms. This is in contrast with high velocity missiles that induce tissue cavitation and injure solid, inelastic organs such as the liver and spleen.[6]

Results have shown that civilian gunshots to the anterior abdomen enter the peritoneal cavity in 80% of cases and cause significant visceral injury in 95% of patients.[1] Thus laparotomy is usually performed for gunshot wounds that penetrate the peritoneum (as indicated by physical examination and/or biplanar x-ray). As mentioned above, more recently a selective approach to laparotomy for gunshot injuries, similar to that for stab wounds has been suggested, but is contraversial.[3]

DIAGNOSTIC PERITONEAL LAVAGE (DPL)

DPL has been used in the past as a safe and inexpensive method for rapidly identifying life threatening intraperitoneal injuries. It is being less relied upon with the advancement of ultrasound and computed tomography (CT). Briefly the procedure for DPL is to infuse 1litre of warmed normal saline into the peritoneal cavity through a catheter inserted via a small incision midway between the umbilicus and symphysis pubis. If the patient's condition permits, side-to-side movement can enhance sampling. The saline bag is then lowered to the floor for the return of lavage fluid by siphonage, after which it is sent to the laboratory for analysis of red cells, white cells, amylase, alkaline phosphatase and for the presence of bile. It has been suggested that using a threshold of over 1000RBC/mm^3 as an indication for laparotomy reduces the number of unnecessary operations an the overlooked injury rate.[1]

It must be remembered that some gas-

trointestinal perforations may become isolated leading to false negative results on DPL. Thus patients with a negative lavage should be admitted for observation for twenty-four hours, and undergo prompt laparotomy if signs of peritoneal irritation ensue.

PLAIN FILM OF ABDOMEN

The advantage of plain film x-rays are their virtual universal availability in hospital accident and emergency departments. Obtaining films in two planes allows localisation of the penetrating object. It may also reveal the presence of free air (on erect or lateral decubitus films), indicating bowel perforation and thus dictating the need for immediate laparotomy.

COMPUTED TOMOGRAPHY (CT)

CT imaging is continually improving with greater experience and technological advances. In the setting of penetrating abdominal trauma it is particularly useful for assessment of injuries to the retroperitoneum, when DPL is of no benefit.

LAPAROSCOPY

The application of laparoscopy to abdominal trauma was received with great enthusiasm. However, the requirements of a pneumoperitoneum and the possibility of missing injuries have meant that it has not been widely employed. It is likely that in future it will find application in well-defined situations.

EMERGENCY LAPAROTOMY

An emergency laparotomy is usually performed through a midline incision, thus allowing simple extension if greater access is required. The first priority is the control of haemorrhage. All of the abdominal organs must then be systematically and carefully inspected for injury. On completing the laparotomy, a thorough lavage with warm normal saline should be performed, especially if there has been any contamination with intestinal contents.

INFECTIOUS DISEASE

A study by Fullen et al. indicated that pre-operation antibiotics significantly reduced infection rates following penetrating abdominal wounds.[7] Their results showed infection rates of 7%, 33% and 30% if antibiotics were given pre-, intra- or post-operatively, respectively. If the colon was perforated in the injury, these infection rates increased to 11%, 57% and 70%, respectively. The same study advocated the use of broad-spectrum antibiotics. The duration of antibiotic administration for penetrating abdominal injuries was suggested to be twenty-four hours, since no additional benefit was found with prolonged therapy.[8]

An interesting aspect of management of penetrating abdominal wounds is that antibiotics may not reach therapeutic levels in people who are aggressively resuscitated with large volumes of crystalloid. Therefore, it has been suggested that doses should be adjusted depending on the volume of fluids required for resuscitation, to prevent sub-therapeutic treatment.[9] Tetanus prophylaxis should also be given following penetrating abdominal trauma.

CONCLUSION

The management of penetrating abdominal trauma is still evolving. The main challenge is to quickly and reliably differentiate between the patient with life-threatening injuries requiring immediate surgery, and those that can be safely managed conservatively, thus avoiding the potential complications of surgery.

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Barrett's Oesophagus

Parul Dureja

Oesophageal adenocarcinoma has increased in incidence by more the 70% in the last 20 years, and its incidence is increasing more rapidly than that of any other malignancy in the Western world.[1,2] Despite advances in multimodal therapy, the prognosis for invasive oesophageal adenocarcinoma is poor. Barrett's oesophagus is the most significant risk factor for the development of oesophageal adenocarcinoma. The annual risk of oesophageal adenocarcinoma for patients with Barrett's metaplasia is approximately 1%, a figure 30-40 times that of the general population.[1] The management of Barrett's oesophagus is controversial, and it is not yet known whether surveillance for detection of early invasive adenocarcinomas improves survival. An improved understanding of the molecular biology of this disease may allow improved diagnosis, therapy, and prognosis.

DEVELOPMENT OF BARRETT'S OESOPHAGUS

Barrett's oesophagus is defined as the replacement of the distal oesophageal squamous epithelium by specialized intestinal epithelium, characterized by the presence of goblet cells.[1] There is considerable evidence that Barrett's oesophagus is an acquired condition, which occurs as a complication of longstanding gastro-oesophageal reflux of acid and particularly bile. Approximately 10% of patients with chronic gastro-oesophageal reflux disease (GORD) will develop Barrett's oesophagus.[2]

Barrett's epithelium and its malignant transformation occur in a stepwise process from metaplasia through dysplasia to invasive adenocarcinoma, and involve a wide variety of cellular and molecular changes (Figure 1).[1] The process by which specialized intestinal epithelium replaces squamous epithelium is poorly understood. One proposed theory is that longstanding GORD produces inflammation and eventually ulceration of the squamous epithelial lining.[3] The response to cell death and inflammation includes increased folding of the oesophageal epithelium, which results in stem cells becoming more superficial.[1] In the microenvironment of an abnormally low pH in the distal oesophagus, these superficial stem cells may become damaged or die, or they may differentiate into an abnormal columnar epithelium that is thought to be more resistant to injury from refluxing gastric contents.[3]

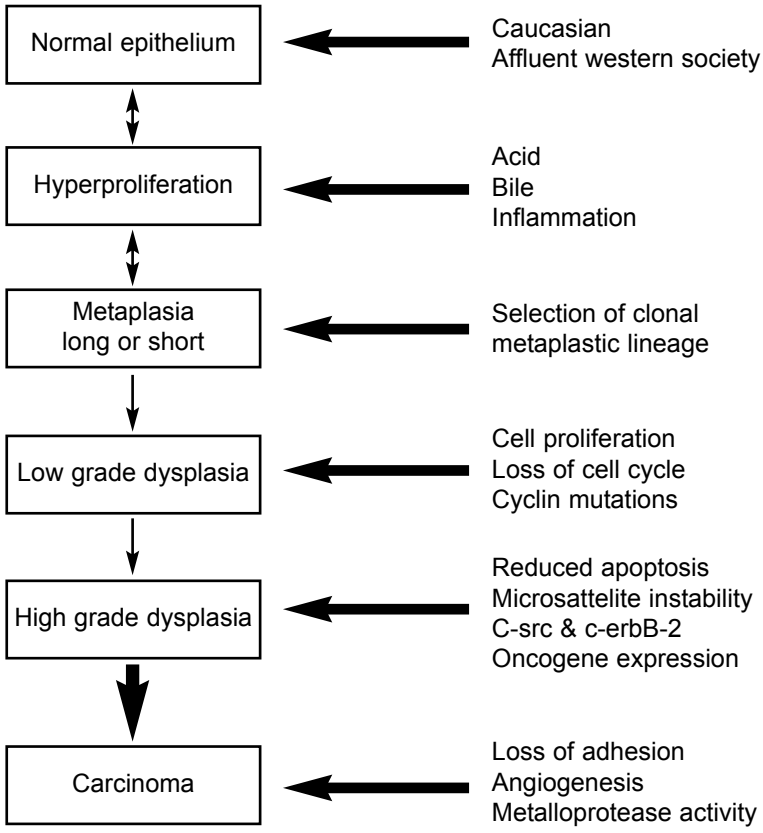

Figure 1. Schematic representation of the proposed metaplasia-dysplasia-carcinoma sequence for the evolution of Barrett's oesophagus and oesophageal carcinoma (reproduced from Aldulaimi et al, *Dis Esophagus* 1999; 12(3):177-80).

MANAGEMENT

The American College of Gastroenterology recommends regular endoscopic surveillance of patients with Barrett's oesophagus.[4] However, surveillance with multiple biopsies is costly and inconvenient, and it remains controversial whether it reduces mortality. The aim is to detect high-grade dysplasia as it is the precursor lesion to adenocarcinoma. The rationale of endoscopic surveillance is to offer oesophagectomy, assuming the patient is fit, either before the development of adenocarcinoma or at an early stage. A selective surveillance policy, aimed at only those at greatest risk, would increase the cost-effectiveness and reduce the endoscopic burden.[2]

There is currently considerable controversy regarding the appropriate management of patients with Barrett's oesophagus. The aim of treatment is more to influence the natural progression of the disease rather than symptom relief, as many patients are asymptomatic owing to reduced mucosal sensitivity.[2] Two studies have shown a lesser influence of acid suppression therapy on the natural course of the disease when compared with antireflux surgery.[2,5] This is attributed to the fact that treatment with high dose proton pump inhibitors (PPI) normalizes oesophageal acid exposure, but is relatively ineffective in reducing bile reflux compared to fundoplication.

Several other factors suggest that surgical management of Barrett's oesophagus may be preferable to long term acid suppression therapy. First, in contrast to acid suppression therapy alone, antireflux surgery corrects underlying defects that are often present in patients with Barrett's oesophagus, such as lower oesophageal sphincter tone, hiatus hernia, and duodenogastro-oesophageal reflux. In addition, successful antireflux surgery offers complete and continuous reflux control. This is especially important as in vitro studies show that intermittent acid exposure causes greater cell proliferation and de-differentiation of Barrett's oesophageal cells than both continuous or no acid exposure.[2] This finding has also been observed in vivo; a study from the Karolinska Institute suggested that acid suppression therapy increases threefold the odds ratio of patients with GORD developing adenocarcinoma.[6] Two studies also show a lower incidence of dysplasia and adenocarcinoma among patients treated with fundoplication versus those treated with acid suppression therapy alone.[7,8]

In recent years, endoscopic ablative techniques have been proposed as techniques to reverse Barrett's oesophagus.[9] A number of techniques (in combination with acid suppression) are being investigated and these include photodynamic therapy (PDT), laser photocoagulation, argon plasma coagulation (APC), electrocoagulation, heater probe, and cryotherapy. The side effect profile of these procedures and confirmation of their potential to produce long-term risk reduction of adenocarcinoma have yet to be elucidated.

CELLULAR AND MOLECULAR CHANGES

An improved understanding has been gained of the polyp-carcinoma sequence in the colon in recent years. Much research is presently being carried out into the metaplasia-dysplasia-carcinoma sequence of the oesophagus, but the precise mechanisms are still poorly understood. Various cellular and molecular changes are involved in the malignant transformation of Barrett's epithelium (Figure 1). These include mutations in the p53 tumour suppressor gene, and alterations in the statement of various oncogenes, such as c-src, c-erbB-2, and c-myc.[1] Recent evidence also suggests a role for abnormalities in cellular adhesion molecules in the development of invasive oesophageal adenocarcinoma. Alterations in the statement of various adhesion molecules are thought to result in a reduction in cellular adhesion, allowing invasion and metastases.[1]

Investigators are currently examining the potential role pro-inflammatory cytokines, namely tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), play in the progression of Barrett's epithelium to adenocarcinoma. It is thought that TNF-α and IL-1 released in response to chronic GORD may mediate their effect through activation of the NF-κB pathway. NF-κB comprises a family of inducible transcription factors that serve as important regulators of the host immune and inflammatory response.[10] The NF-κB pathway is a key mediator of genes involved of cellular proliferation and apoptosis. TNF-α and IL-1 released in response to chronic GORD may activate the NF-κB pathway, thereby inducing the statement of anti-apoptotic genes and establishing a positive feedback loop for their statement. The statement of anti-apoptotic genes may then impair apoptosis and potentiate the effects of increased proliferation of stem cells in Barrett's epithelium.

CONCLUSION

The appropriate management of patients with Barrett's oesophagus remains a subject of great debate. Barrett's oesophagus and its progression to oesophageal adenocarcinoma is associated with a wide variety of mol-

ecular and cellular changes which parallel histological progression from metaplasia through dysplasia to invasive cancer. An improved understanding of these molecular changes may help to target those in need of regular surveillance and could lead to improved treatment in the future.

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Caffeine

Ciara McLaughlin

INTRODUCTION

In a civilised society, the ritual of "going for coffee and a chat" is almost religiously observed. In fact, in industrialised countries coffee is one of the most widely used non-alcoholic beverages. Caffeine is an important component of this drink and has been frequently described as the most widely used drug in the world. A 150ml cup of coffee contains about 60-120mg of caffeine.[1]

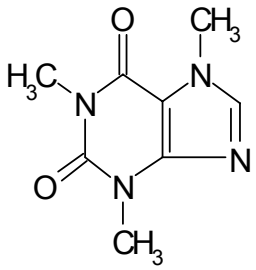
Caffeine is consumed in numerous other forms including tea, soft drinks, cocoa and chocolate. Also, it is found in several medications including over-the-counter cold and allergy medicines, analgesics, appetite suppressants, and stimulants. Therefore, it appears that caffeine has been part of the typical daily diet for many hundreds, if not thousands of years. Other factors that may influence our consumption of caffeine containing beverages include personality traits as well as environmental stressors.

PHARMACOLOGICAL PROPERTIES OF METHYLXANTHINES

Caffeine is an alkaloid and belongs to the methylxanthine group of compounds, of which theophylline and theobromine are also important members. These compounds have different biochemical effects and are present in different ratios in different plant extracts. Caffeine is by far the most popular drug in the group (Figure 1).

Caffeine is readily absorbed from the gastrointestinal tract (GIT) and rapidly distributed in all the body fluids. Ingestion with food does not appear to affect its absorption.[1] In most patients, the drug obeys first-order kinetics within a therapeutic range. At higher concentrations, zero-order kinetics becomes evident as the enzymes involved in its metabolism are saturated.[2] The half-life of caffeine is approximately 3.5 hours, although in overdose this can increase up to 9 hours.[3] The half-life is prolonged by factors such as being pregnant, being on oral contraceptives and having liver disease.[4] Smoking and hepatic microsomal enzyme inducers, like phenobarbital, reduce the half-life of caffeine.[3] Caffeine is excreted in the urine as 1-methyluric acid, 1-methylxanthine and an acetylated uracil derivative.[4] Both genetic and environmental factors influence the considerable inter-individual variability that exists in the rate of caffeine elimination.

Figure 1.
Caffeine: 1,3,7-trimethylxanthine



The methylxanthines have effects on the central nervous system (CNS), kidney, cardiovascular system, and skeletal and smooth muscle (see below). Gastrointestinal disorders, tremor, headache and insomnia are among a number of adverse effects that can occur. Methylxanthines can induce palpitations and even cardiac arrhythmias.[4]

Caffeine is a non-selective antagonist of adenosine at both A1 and A2 adenosine cell surface receptors. A1 receptor stimulation inhibits the release of noradrenaline at the sympathetic smooth muscle junction, whereas A2 receptors have a direct vasodilatory effect.[5] Methylxanthines can be shown, in vitro at high concentrations, to inhibit the enzyme phosphodiesterase causing a hydrolysis of cyclic nucleotides. This inhibition leads to higher concentrations of intracellular cAMP. This effect could explain the cardiac stimulation and smooth muscle relaxation produced by methylxanthines, but the topic remains somewhat controversial. Methylxanthines also have direct and indirect effects on intracellular calcium concentrations. This uncoupling of intracellular calcium increases with muscle contractile elements.[2]

PHYSIOLOGICAL EFFECTS OF METHYLXANTHINES

At low to moderate doses, methylxanthines can affect the CNS causing a mild cortical arousal with increased alertness and deferral of fatigue. In unusually sensitive individuals, the caffeine contained in a single beverage is sufficient to cause nervousness and insomnia. At very high doses, medullary centres are stimulated, and focal and generalised convulsions may occur. Methylxanthines can also impact the musculoskletal system demonstrated by an increase in the strength of isolated skeletal muscle contractions in vitro. They have potent effects on the contractility of the diaphragm and they reduce diaphragmatic

fatigue in both normal subjects and in those with a chronic obstructive pulmonary disorder (COPD). The methylxanthines can also have a relaxation effect on various types of smooth muscle, consequently producing a major therapeutic action of bronchodilation. Another important physiological effect of methylxanthines is an increase in the production of urine. It is suggested that this effect is related to the increase in both renal blood flow, especially in the medulla, and the glomerular filtration rate.[5]

THE CARDIOVASCULAR EFFECTS OF CAFFEINE

Caffeine can affect the cardiovascular system through a variety of mechanisms (Table 1).[2,5] The findings of caffeine's effects on the cardiovascular system are confounding and many are inconsistent among studies.

For example, the administration of 250-300 mg of caffeine to methylxanthine-naive individuals may produce small decreases in heart rate but such doses usually have no effect on those who drink caffeine regularly. The caffeine-induced lowering of heart rate may be a refractory bradycardic response to pressor action or a direct effect on the cardiac or sino-atrial node (SAN). There is controversy as to whether circulating catecholamines or plasma-renin activity increases significantly in caffeine-naive subjects, however, it is generally agreed that little change occurs in chronically exposed individuals.[2,5] In unusually sensitive individuals consumption of a few cups of coffee may result in arrhythmias, but in most people parenteral administration of higher doses of methylxanthines produces only sinus tachycardia and increased cardiac output.

SHORT TERM VASCULAR EFFECTS OF CAFFEINE

After acute intake of caffeine, increased systolic and diastolic blood pressure levels have been detected.[5] Acute intake of caffeine increases vascular resistance, indicating a vasoconstrictor effect. It seems that caffeine plays an active role in this vasoconstriction effect since regular coffee intake has a tendency to increases blood pressure, whereas regular intake of decaffeinated coffee appears to have little or no effect.[6] A 200-250 mg dose of caffeine (2-3 cups of coffee) increases systolic blood pressure by 3-14 mmHg and diastolic blood pressure by 4-13 mmHg in normotensive subjects.[5] The pressor effect correlates with increases in plasma caffeine concentrations. Caffeine-induced increases in blood pressure may last for 4 hours or longer.

Table 1: Important Mechanisms Effecting Cardiovascular System

Antagonistic effects on adenosine receptors
Inhibition of phosphodiesterase (increase in cyclic nucleotides)
Activation of the sympathetic nervous system (release of catecholamines from the adrenal medulla)
Stimulation of adrenal cortex (release of corticosteroids)
Renal effects (diuresis, natriuresis, activation of the renin-angiotensin-aldosterone system)

Hypertensive or hypertension-prone subjects seem to have a more pronounced acute pressor response to caffeine than normotensive subjects.[7,8] Also, individuals experiencing mental and physical stress appear to exhibit the pressor effect of caffeine, which suggests that the response is additive or enhanced. It has also been suggested that the pressor effect of caffeine is stronger in older subjects than in the young.[9] Finally, people who do not normally consume caffeine tend to experience a stronger pressor effect with acute caffeine intake than frequent consumers of caffeine. The degree of blood pressure response associated with a single dose of caffeine seems to be inversely related to the plasma caffeine concentration at the time of administration.[5]

CHRONIC CAFFEINE INTAKE AND BLOOD PRESSURE

The evidence for long-term effects on blood pressure is inconclusive to say the least. Some long-term studies have shown that caffeine induces persistent pressor effects in habitual consumers, often as much as 6mmHg. It has been found that changing from caffeinated to decaffeinated coffee results in a slight fall (2-5mmHg) in blood pressure[5]. A Brazilian study found that the hypertensive effect of caffeine disappeared with chronic use in young adults.[7] However, many other epidemiological studies reported that chronic caffeine consumption or abstinence from caffeine was not accompanied by significant changes in blood pressure.

A large study, of male self-defence officials in Japan, found that habitual coffee drinkers in the group had lower blood pressure than non-drinkers regardless of alcohol use, cigarette smoking, obesity and glucose intolerance.[6] Another study found that regular consumption of coffee appears to be positively associated with an increased risk of thromboembolic stroke in middle-aged hypertensive

men.[5] A study of 45,589 American men between the ages of 40-75 years without any history of cardiovascular disease were assessed to determine the relationship of coffee consumption with the risk of myocardial infarction and the possible risk of stroke.[10] In this case, the findings indicated that the use of caffeinated coffee and the total intake of caffeine did not significantly increase the risk of coronary heart disease or stroke.

TOLERANCE TO CAFFEINE

The development of tolerance may explain the failure to detect an increase in blood pressure caused by repeated administration of caffeine.[5] After regular intake of caffeine, the pressor response has been reported to decrease within a few days. However, in some studies caffeine was still able to elevate blood pressure during habitual consumption, suggesting that tolerance may only play a partial role in the pressor reponse. Also, the pressor response to caffeine may be regained after a relatively short period of abstinence. For example, caffeine ingested after an abstinence of 10-12 hours was shown to increase blood pressure in regular coffee drinkers. A pressor response to a second cup of coffee of the day has also been observed. It is possible that there are people at either end of the spectrum: those who have a higher sensitivity to caffeine and those with lesser susceptibility to the development of tolerance.

One study was carried out to determine the blood pressure response during exercise between individuals who regularly consumed caffeine and those who did not consume caffeine. Caffeine consumption resulted in significant increases in both systolic and diastolic blood pressures at rest and during exercise. No differences were observed between those who were habitual consumers and those who regularly abstain from caffeine.[8]

It is interesting to note that chronic caffeine users who become tolerant to the effects of caffeine may be seen to experience withdrawal in its absence. Typically this abstinence syndrome takes the form of headaches, increased sleepiness and decreased alertness.[1] The psychiatric literature describes associations of caffeine use with a syndrome of anxiety, depression, and even psychosis.[11] Recently, a caffeine dependence syndrome has been characterised by withdrawal, tolerance, and failure to control use despite the knowledge that it is likely to be contributing to an existing physical or psychological problem.[12] Several studies have also suggested possible associations with osteoporosis ulcers and cancer.[13,14,15,16]

POSSIBLE ROLE OF CAFFEINE IN HYPOERTENSON

Five hypertension risk groups (optimal BP, normal BP, high-normal BP, stage 1 hypertension, diagnosed hypertension) were the focus of a study on the acute effects of caffeine.[17] The study indicated that, while all groups exhibited increases in both systolic and diastolic blood pressures, the strongest response to caffeine was among the diagnosed hypertension group, followed by the stage 1 and high-normal groups and then by the normal and optimal groups.

The effects of caffeine on blood pressure and cortisol secretion were examined during a period of elevated work stress in male medical students.[18] These groups consisted of individuals with high and low risk factors for hypertension and were regular consumers of coffee.[8,19] The study found that stress and caffeine resulted in additive increases in blood pressure. Therefore, it has been recommended that individuals at high risk for hypertension should refrain from the use of caffeinated products, especially during periods of heightened stress.[19]

The effects of rest and exercise in relation to caffeine intake and the affect on pressor regulation in men at risk of hypertension were investigated.[19] Conclusions drawn from this study indicated that restriction of caffeine before exercise could benefit persons who are at risk for hypertension or who have an unusual sensitivity to caffeine.

In hypertensive subjects the combination of coffee and smoking produced a stronger and more sustained pressor response than each stimulus alone.[5] Moreover, in a cross-sectional observational study using 24-hour ambulatory blood pressure monitoring, moderate smokers and coffee drinkers with mild hypertension had significantly higher daytime blood pressure than non-smokers and those who did not drink coffee. This suggests that the effect might recur throughout the day, despite the increased caffeine catabolism in smokers.[5]

Mahmud and Feely have found that caffeine acutely stiffens the aorta and impedes the function of the peripheral vascular arteries.[20] This may be an important vascular mechanism for the hypertensive effect of caffeine.

SUMMARY AND CONCLUSION

Caffeine has variable effects on the cardiovascular system depending upon the usage (acute or chronic) and the disposition of the individual. The factors that affect individ-

ual disposition include: age, pregnancy, hypertension-status, burden of stress, smoking status, and caffeine tolerance. In general, acute intake of caffeine increases systolic and diastolic blood pressure levels. The pressor effect correlates with increases in plasma caffeine concentrations, and has been enhanced during times of mental and physical stress. Those who are caffeine-naive tend to experience a stronger pressor effect with acute caffeine intake than habitual consumers.

The information available regarding the effects of chronic caffeine intake on blood pressure was inconclusive. Whereas some long-term studies suggest that caffeine induces a persistent pressor effect in the habitual consumer, other studies suggest chronic caffeine consumption is not accompanied by significant changes in blood pressure.

One study concluded that consumption of coffee appeared to be positively associated with an increased risk of thromboembolic stroke in middle-aged hypertensive men. Another study indicated that the use of regular coffee and the total intake of caffeine did not appreciably increase the risk of coronary heart disease or stroke.

Hypertensive or hypertension-prone subjects seem to have a more pronounced pressor response to caffeine than normotensive subjects. Studies concluded that restriction of caffeine, before exercise and during times of heightened stress, could benefit persons with risk for hypertension or unusual sensitivity to caffeine. The combination of coffee and smoking in hypertensive subjects produces a stronger and more sustained pressor response than each stimulus alone.

Although some of the information available regarding the long-term vascular effects of caffeine is conflicting, the overall conclusion would be that anyone who smokes or has risk factors for hypertension should try to avoid caffeine products as much as possible.

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Why is Retreatment Less Successful than Conventional Root Canal Treatment?

Padhraig Fleming

INTRODUCTION

Endodontic therapy is one of the most progressive aspects of modern dentistry. Significant advancements in debridement and obturation techniques have occurred in recent years. Consequently, success rates approaching 90% have been reported.[1] However, endodontic procedures can be among the most technically challenging faced by many dentists. Root fillings can, and do fail and failures necessitate retreatment. Likewise, asymptomatic root fillings occasionally require retreatment prior to elaborate prosthodontic procedures, as endodontic failure may follow expensive restorative work. Success rates for conventional endodontic treatment are often reported at 80-85%.[2-4] Factors dictating success or failure include[5] the presence of pre-operative periapical radiolucency,[4] the apical extent of filling,[3] the quality of obturation, the observation period,[2] any iatrogenic complications and post-endodontic restoration.[6]

Follow-up studies on endodontically retreated teeth having pre-operative rarefactions report markedly lower success rates of 47-77%.[4,7-8] Interestingly, however, teeth retreated for technical or restorative reasons enjoy very high success rates of 93.8-98%, illustrating the importance of pre-operative periapical status in governing endodontic success or otherwise.[4,7-8]

WHY DO ROOT CANAL FILLINGS FAIL?

Intra-radicular Bacteria

These are considered causative in over 80% of cases. Micro-organisms colonizing root canals play a vital role in the pathogenesis of periradicular lesions. Sundqvist first proved this role in vivo.[10] He discovered that bacteria were only detected in root canals of pulpless teeth with periapical bone destruction. Causes of residual intra-radicular bacteria include incomplete debridement, coronal leakage and missed canals.[11]

Extra-radicular Bacteria

Some bacterial species are capable of survival outside the root canal in the periradicular tissues thereby inducing peri-apical pathology. *Actinomyces* species and *Propionibacterium propinicum* may be implicated in extra-radicular infection.[12,13] Bacterial organisation into biofilms may also permit their evasion of host defences.

True Cysts

Ramachandran Nair used sectioning techniques to examine peri-apical lesions. He deduced that 15% of these lesions were, in fact, cysts. He further sub-divided cysts into "true" or "bay." Bay cysts communicate with the root canal. However, true cysts do not. Thus, they are refractory to even technically excellent conventional or orthograde retreatment approaches. Surgical retreatment is necessitated in this situation. This theory is not accepted universally, however.

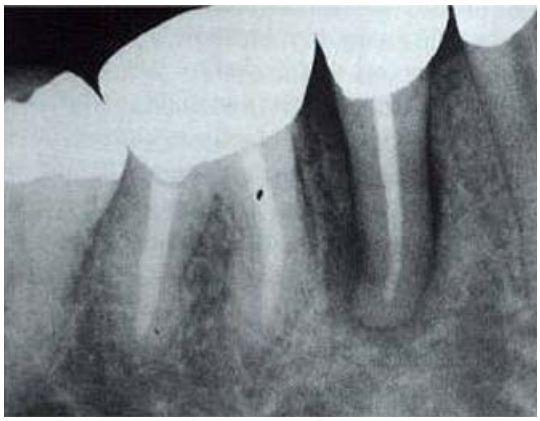
Extra-radicular Foreign Materials

Rarely, endodontic procedures may fail because of intrinsic or extrinsic non-microbial factors. Foreign body reactions against cholesterol crystals derived from disintegrating host cells have been implicated in failure.[14] Extrinsic factors include talc in gutta-percha cones, cellulose components of paper points and cotton wool if extruded into the peri-apical tissues.[15,16] Leaving a tooth in open drainage is also ill advised. Complications arising from these teeth are often very difficult to treat.

Undiagnosed Vertical Root Fracture

Such teeth are often misdiagnosed as endodontic failures. The prevention of unnecessary and inevitable endodontic failure in these retreatment cases resides in careful history-taking, examination and diagnosis. The use of diagnostic aids, such as microscopes, radiographs (Figure 1), periodontal probing, tooth slooth, dyes, transillumination and, occasionally, surgical exposure, is crucial in these cases. According to Chong and Pitt-Ford, the basic difference between root canal retreatment and initial root canal treatment is the need to remove the previous root filling before a tooth can be retreated.[17] This suggestion may be over-simplistic as removal of old restorations is one of a number of different challenges

Figure 1. Example of a radiograph. Note the radiolucent "halo" surrounding mandibular second premolar suggestive of a root fracture.



encountered in retreatment cases (e.g. different microflora, negotiation of procedural errors and overcoming aberrant anatomy).

GAINING ACCESS

Occasionally posts must be removed from teeth having insufficient coronal tooth structure to support a workable coronal restoration for endodontic or prosthodontic reasons. Post removal may be achieved by, ultrasound, post-removing devices (e.g. Post puller, Gonon post removal system), masserann instrument (this is associated with a 55% success rate, is less successful in posterior teeth and is very time-consuming.[19]), or drilling with a bur.[17] These procedures are often quite technically demanding, cumbersome and are associated with significant morbidity.

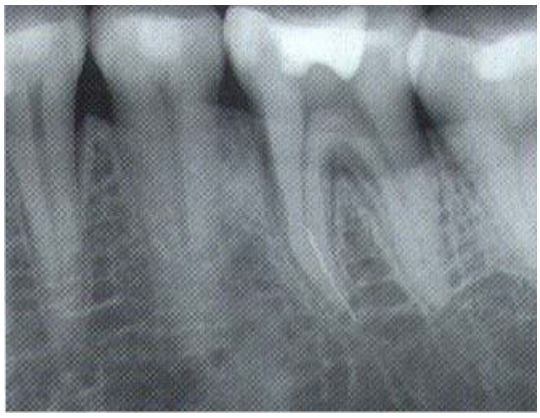
Other materials sometimes requiring removal include silver points, gutta percha, thermafil, paste and cement, and broken instruments (Fig. 2). Silver points tend to be extremely difficult and tome-consuming to remove as are broken instruments.[20] Some cements for example SPAD, which sets harder than dentine, and AH26 are particularly difficult and often impossible to remove. Removal is thus fraught with danger and surgery may be a more sensible option in selected cases.

However, with careful case-selection and thorough mechanical and chemical debridement, stainless steel files may often be left in situ without greatly affecting the prognosis [21,22].

These procedures must be performed with great care as a number of undesirable complications may occur including root fracture, file fracture, the removal of excess root dentine predisposing to future fracture, canal perforation, and extrusion of objects beyond root apex.[23]

Without due care and attention catastrophic failures may ensue. I believe many of these early failures are not included in the clinical studies documenting success rates for retreatment procedures.[4,7,8]

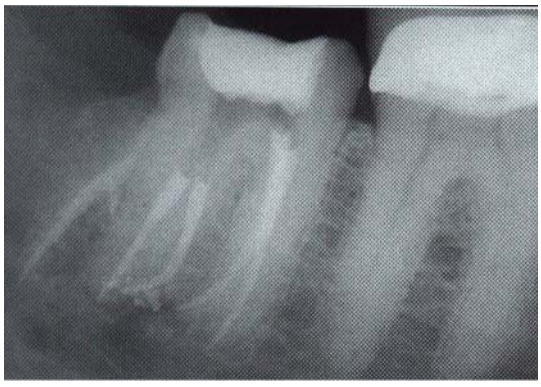
Figure 2. Broken instrument in apical one third of mesial root of a mandibular first molar.



ANATOMIC VARIATION

Missed canals are a common cause of root canal treatment failure as they often harbour bacteria and related irritants contributing to clinical symptoms. Aberrant or unusual anatomy must be considered in retreatment cases. Because the success rates of endodontic procedures are now so high we must expect unusual anatomy or some other mitigating factor as contributory particularly if the obturation appears satisfactory radiographically i.e. dense, 3D obturation of the canal system to within 1mm of the radiographic apex. Several roots have additional canals (Fig. 3).[24] For example: maxillary first molars which often (78% of cases approximately) contain 2 canals in the mesio-buccal root [25]; maxillary first premolars which are occasionally three-rooted. Each root contains a separate canal[26]; mandibular incisors which contain two canals in over 40% of cases[27]; and mandibular first molars which contain four canals in approx.

Figure 3. Five canals in a mandibular second molar.



one third of cases.[28]

Anatomic familiarity is essential before re-entering a root canal-treated tooth. Other aids in detection include radiographic analysis (Canals are generally "centered" in the root. Therefore, deviation from the mid-root is often an indication of the presence of a second system.), digital radiographs, magnification (An operating microscope with supplementary illumination facilitates the localization of "missed" canals and the removal of canal obstructions[29]), expanded access cavities (Isthmus areas should be probed with explorers in an effort to detect a "catch" suggestive of another orifice.), ultrasonics, micro-openers, dyes (for example methylene blue, which may be used to "roadmap" anatomy), and sodium hypochlorite. The clinician must be aware of root canal complexities. They must expect the unexpected where root canal morphology is concerned. This approach is particularly warranted in retreatment cases.

THE MICROBIOLOGY OF ROOT CANAL THERAPY FAILURE

The microbiology of root canals exhibiting failing endodontic therapy is markedly different from that of an untreated canal.[30,31] The latter is often a mixed infection, in which gram-negative anaerobic rods predominate. The former is usually composed of 1-2 species, generally gram-positive bacteria. In particular levels of *Enterococcus faecalis* are raised. In Sundqvist's study[31] 38% of failing canals harboured the bacterium. Increased proportions of *E. faecalis* in teeth lacking adequate seal during treatment or treated over more than ten visits have been reported[32] supporting the suggestion that *E. faecalis* enters the canal during treatment. *E. faecalis* strains have shown resistance to intra-canal medicaments for example calcium hydroxide.[33] Therefore this bacterium commonly appears in refractory cases, usually as the single species of microorganism present. Consequently, endodontic retreatment is very prone to failure in these specific cases. Yeast-like microorganisms have also been isolated from failing root fillings.[34] Like *E. faecalis* some *Candida* species are resistant to commonly deployed intra-canal medicaments. Therefore, the microflora of failing endodontic fillings may be extremely resistant and difficult to eradicate thereby predisposing to infection and thus, failure of retreatment. Modified and more potent intracanal medicaments may be required to enhance the elimination of resistant bacteria in these retreated canals.

OVERCOMING PROCEDURAL ERRORS

Procedural errors performed during the initial root canal treatment of an infected tooth may predispose to failure. Procedural accidents often impede or render it impossible to accomplish effective intra-canal procedures.[35] These iatrogenic factors must often be overcome to effect successful retreatment, which is obviously more demanding than conventional root treatment.

Blocked canals are often encountered in retreatment cases. Attempts to get to working length and allow thorough cleaning of the whole root canal system are painstaking. These procedures require perseverance and patience. Copious full-strength (5.25%) sodium hypochlorite irrigant may be used in combination with pre-curved, narrow files used in an apically directed picking motion to loosen the material. Viscous chelators may also be used to work the file to length. This procedure is often very difficult and fails. In such instances, regardless of the quality of obturation, the patient must be informed of the likelihood of endodontic failure (particularly if the previous filling failed clinically). Consequently, inadequate initial mechanical debridement may reduce the prognosis of initial root treatment and decrease the likelihood of successful retreatment if necessitated.

Ledges represent an internal transportation of the canal. They may be bypassed using the same techniques as used for "blocks".[36] Ledges may be reduced or removed using Greater Taper Ni-Ti files. However, clinicians must be wary of removing excess dentine in an attempt to completely remove the ledge.

Another problem often encountered in retreatment cases is apical transportation. Canals exhibiting apical transportation tend to be internally underfilled. Mild transportations may be dealt with by simple cleaning, shaping and obturation. Again, however, extra root dentine may be sacrificed predisposing to subsequent root fracture. Moderate transportation may be negotiated using mineral trioxide aggregate (MTA).[37] Severe transportation, however, carries an almost hopeless prognosis if using conventional retreatment means. Hence, retrograde means are needed to ensure success. In this instance case selection is vital in ensuring success of endodontic retreatment, which has been affected adversely by careless initial treatment.

Root perforation is a procedural error that can have a profound effect on the prognosis of treatment.[38] Perforations are a common cause of endodontic failure.[39] Hence, they are

regularly encountered in retreatment cases. It has been claimed that non-surgical treatment of perforation is limited because of the difficulty in determining the perforation's location, shape and size in addition to the lack of matrix against which the sealing material can be packed without excess spreading to the periradicular tissues.[40] Materials used in perforation repair include calcium hydroxide, amalgam, intermediate restorative material, composite resin and gutta percha. The use of biocompatible matrices e.g. tricalcium phosphate or hydroxyapatite, have been proposed in order to control the extrusion of repair material.[41] More recently MTA has been deployed in perforation repair. It has been claimed that MTA affords a biocompatible immediate seal to the perforation site with optimum healing.[42] Undoubtedly, however, despite this recent advance perforations do represent a mitigating factor likely to affect adversely success rates of endodontic retreatments.[43]

SURGICAL ENDODONTIC RETREATMENT

Surgical retreatment carries a considerably lower success rate than conventional retreatment.[4] Guttman and Harrison report success rates of 25-90%.[44] However, endodontic surgery is specifically indicated in the following situations: failed orthograde treatment where access to the canal is impossible conventionally; obstructed canals in a symptomatic tooth; apical perforations failing to respond to repair material for example MTA; grossly over-extended filling material in a symptomatic tooth; and horizontal fracture at the apex in a symptomatic tooth.

In the above cases conventional retreatment should be carried out if possible to eliminate bacteria and related irritants from the root canal system. This approach prevents the likelihood of placement of a "lid on a sewer".[45] Zuolo, Ferreira and Guttman[46] reported success rates of 91.2% overall for surgical treatment preceded by orthograde retreatment. The importance of conservative retreatment was shown in another study where there was a 24% higher retreatment success rate in cases of failed endodontic therapy in which antibacterial measures and refilling of the canal preceded apical surgery, than in cases in which apical surgery was the only treatment performed, was reported.[47]

CONCLUSION

Overall, retreatment is less successful than primary root canal treatment. Retreatment procedures are complicated by difficulties in accessing canals to allow effective cleaning and shaping of the system, overcoming procedural errors, aberrant anatomy and an increasingly resistant microflora. Candidates for retreatment are likely to be very "dentally aware" as they have already had initial root treatment. Consequently, patient education and case presentation are vital. Patients should be informed that retreatment carries a poorer prognosis (particularly if symptomatic at the outset) and complications may arise necessitating surgery or removal of the tooth. Clinicians must consider specialist referral in particularly difficult cases. However, careful case selection, examination, trouble-shooting and endodontic work can guarantee success even in complicated retreatment cases.

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Sickle cell disease in Pregnancy: A new consideration for the Irish Obstetric and Neonatal Service

Thato Mabote

INTRODUCTION

Sickle cell disease is a haemoglobinopathy occurring as a consequence of the presence of sickle haemoglobin. It is a recessive disorder in which the sickle haemoglobin molecule is made up of two normal alpha chains bound to two abnormal beta chains (s chains). Several distinct genotypes of the disease process have been described. Homozygous sickle cell (SS) disease and sickle cell haemoglobin C (SC) disease are the most common whereas sickle cell-beta+ (Sβ+) thalassaemia and sickle cell-beta^o (Sβ^o) thalassaemia are uncommon genotypes. Other genotypes are very rare.

The disease causes significant morbidity and mortality in those affected, in the first three years of life and especially in the first year of life. Furthermore, pregnant women with sickle cell disease and the developing fetus are at a higher risk of severe life threatening complications. Early diagnosis is therefore essential and is the cornerstone to implementation of prophylactic programmes and successful management of these patients.

EPIDEMIOLOGY

The disease is endemic in people of African descent as well as in Asians and Indians. It is more especially prevalent in tropical zones of the world such as West Africa, where it is thought to confer some protection against malaria. Homozygous sickle cell anaemia occurs in approximately one in 626 African Americans.[1] A study in Jamaica reported SS disease to occur once in every 300 births and SC disease once in every 7000 births.[1] Since the arrival of the immigrant population in Ireland a significant number of cases of sickle cell anaemia have been managed in Irish hospitals.

GENERAL CLINICAL MANIFESTATIONS

Sickle cell disease is a multisystem disorder which may be complicated by splenic dysfuntion syndromes such as pneumococcal septicaemia, acute splenic sequestration andchronic hypersplenism. Massive haemolysis resulting in aplastic crisis and megaloblastic changes in the blood due to the increased demands for folic acid may also result. Bone pathology such as dactylitis, avascular necrosis of bone, femoral head necrosis and osteomyelitis are recognised complications of the disease. Gastrointestinal manifestastions include painful abdominal crisis characterised by diffuse tenderness, abdominal distention, reduced or absent bowel sounds, ileus, and sometimes fluid levels of radiology. The disease may be further complicated by acute chest syndrome which is the largest single cause of mortality from SS disease at all ages. It is characterised by episodes of pleuritic chest pain and shortness of breath. Other recognised features include leg ulceration, nocturnal enuresis, cerebrovascular accidents occurring predominantly in childhood, proliferative sickle retinopathy secondary to vaso-occlussion in the peripheral retina. Morbidity from the disease is highest in the 6 months to 1 year age group and as such may subsequently result in failure to thrive, delayed puberty or even death.[2]

CLINICAL MANIFESTATIONS PARTICULAR TO PREGNANCY

Maternal Complications

Expectant mothers are at a higher risk of frequent acute splenic sequestration and aplastic crisis resulting in rapid onset of profound anaemia (haemoglobin less than 4 g/dl), megaloblastic changes in the blood (because the accelerated erythropoiesis in SS disease increases demand for folic acid which is also necessary in pregnancy), infections (because of impaired splenic function), and venous thrombosis (following the painful vaso-occlussive crisis).

In a review of 68 cases in Guadelope, there were severe complications especially in homozygous sickle cell disease. Painful vaso-occlusive crisis affected 88% of the SS pregnancies and 27% of the SC pregnancies.[3] The pregnant woman is also at a higher risk of pre-eclampsia, acute chest syndrome and death. The rate of Caesarean section in 'sickle cell pregnancy' is higher than in the general population. In the Guadelope study, it was reported

to be 48% higher.[3]

Fetal Complications

The developing fetus is more predisposed to intrauterine growth restriction as a consequence of placental insufficiency, which results from sickling of erythrocytes and vaso-occlussive episodes in the placental circulation. Megaloblastic red blood cells also inadequately deliver oxygen to the fetus, which is at increased risk of neural tube defects because of the increased consumption of folate. The unfavourable in-utero conditions may further predispose to preterm labour. Twenty-one percent prematurity was reported in the Guadelope study.[3] At the extreme end of the spectrum intrauterine death and abortion may occur.

DIAGNOSIS

Sickle cell disease may be diagnosed antenatally as well as in the neonatal period.

Antenatal diagnosis

The diagnosis of SS disease may be made in the first trimester of pregnancy (first 8 to 10 weeks).[4,5] Diagnostic fetal specimen may be obtained by chorionic villus sampling or by amniocentesis.[6] Chorionic villus sampling involves biopsy of the trophoblast, using a small needle passed via transabdominal route or vaginal route into the placenta. It may be performed as early as 6 to 8 weeks but is usually delayed until 10 weeks. Amniocentesis involves extraction of amniotic fluid using a fine gauge needle under ultrasound guidance. It may be performed as early as 10 weeks gestation. The small amount of DNA obtained is then amplified by polymerase chain reaction (PCR).

It is worth noting that both methods are expensive, require technical expertise and relatively sophisticated DNA technology. Furthermore they carry an inherent risk of miscarriage, chorionic villus sampling more so than amniocentesis.

Neonatal diagnosis

Electrophoresis of fetal blood samples on cellulose acetate followed by confirmation on agar gel is most widely used diagnostic tool.[7] Blood samples may be obtained from the umbilical cord or by heelprick. Dried samples on filter paper may be sent by post to a central laboratory. Repeating the procedure after 2-3 months confirms the diagnosis.

Neonatal diagnosis is cheaper than antenatal diagnosis. It is accurate and is suitable for population screening. Given its timing, it offers the option of early introduction of prophylactic programmes, such as penicillin prophylaxis for pneumococcal septicaemia.[8,9] On the other hand, antenatal diagnosis is expensive and hardly applicable on a population-wide basis though it offers the option of early termination of pregnancy.

MANAGEMENT OF SICKLE CELL DISEASE IN PREGNANCY

General Principles

The pregnancy should be considered 'high risk' and antepartum care should preferably be specialist led, so as to deliver optimal care. Intensive maternal and fetal surveillance should be undertaken. Regular exchange blood transfusions, screening for infection and maintenance of hydration are desirable. Folic acid supplements are necessary while Iron supplements are avoided because of the risk of Iron overload. The high risk fetus should be monitored for early signs of compromise and intervention executed at a clinically calculated time, balancing the risks of in-utero compromise and potential distress to those of intervention and prematurity. During episodes of sickle cell crisis, the patient should be admitted and given specialist care. Anti-D antibodies should be given to Rhesus negative expectant mothers in anticipation of possible preterm labour. Steroids should be administered between 24 and 34 weeks gestation to promote fetal pulmonary maturity. Clinical deterioration will prompt delivery.

Maternal and fetal well-being

Optimal care for the expectant mother includes regular screening for infections by performing full blood count and vigilance for indicators of infection, prophylaxis and treatment of infection when indicated, maintenance of adequate hydration as well as regular exchange blood transfusions in women who are profoundly anaemic.[10] Folic acid supplementation is mandatory to prevent the tendancy to megaloblastic changes in the blood and to prevent the relatively increased risk of neural tube defects in the fetus.

Fetal surveillance includes simple records of fetal movements which give a crude but valuable information on fetal activity, ultrasound assessment of fetal growth where the abdominal circumference and the biparietal diameter are measured at 2 week intervals and plotted on centile charts to assess the rate of growth and to differentiate the healthy small fetus from the 'growth restricted' fetus, ultrasound assessment of the biophysical profile where limb movements, tone, breathing move-

ments and liquor volume are assessed and each scored out of two to a total out of eight.[6] A low score suggests severe fetal compromise. Other measures of fetal surveillance are doppler umbilical artery waveforms which aid to identify the 'small-for-dates' fetuses that are growth restricted, doppler uterine artery waveforms performed at 24 weeks gestation to identify pregnancies which are at risk of adverse neonatal outcome, as well as carditocography where the fetal heart rate is recorded electronically. Abnormalities here represent a late stage in fetal compromise and delivery is indicated.

SUMMARY

With the increasing immigrant population in Ireland, sickle cell disease will become common. Similarly the number of pregnancies and births which will be affected is bound to increase. 'Sickle cell disease pregnancy' is a high risk maternofetal situation which needs multidisciplinary specialist care to deliver optimal care, which is so crucial for both the maternal and fetal well being. Early diagnosis remains essential for prophylaxis against early complications. Development of specialist services dealing with diagnostics, screening procedures, genetic counselling, prenatal diagnosis, education and treatment of various haemoglobin disorders such as sickle cell disease seems to be the likely step in the future, in order to deliver optimal care.

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Anti-Tumour Necrosis Factor-alpha Therapy in Crohn's Disease: Clinical and Health Economic Aspects

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ABSTRACT

Objectives: Crohn's disease is a chronic, relapsing inflammatory disease of the gastro-intestinal tract. Tumour necrosis factor-alpha (TNF-α) is a pro-inflammatory protein that is believed to play a major role in the pathogenesis of Crohn's disease (CD). Infliximab, a chimeric anti-TNF-α proclonal antibody, which inhibits the bioactivity of TNF-α, is a recent and exciting strategy in the treatment of CD. The purpose of this study was twofold. Firstly, the economic impact of infliximab therapy was examined. Secondly, chronic active Crohn's disease patients were analysed for their response to infliximab therapy. **Patients and Methods:** The medical records of 25 patients from the Department of Gastroenterology, AMNCH (Dublin) were analysed. Health-care utilization data were collected for each patient over the two years pre- and post-infliximab therapy. The medical records of all chronic active patients were analysed to investigate the role of infliximab as a steroid-sparing agent. The CDAI (Crohn's Disease Activity Index) was employed as a reference for evaluating disease activity. **Results:** Following initiation of therapy with infliximab, the total number of hospital admissions decreased by 46.9%. The mean duration of hospital stays remained unchanged. The mean daily dosages of prednisolone decreased over the 12 months post-infliximab therapy, compared with the 12 months prior to therapy. Similarly, the mean daily dosage of budesonide decreased in the 12-month period following initiation of infliximab therapy. **Conclusion:** The findings from this study of 25 patients with chronic active CD are comparable to those previously achieved in the controlled setting of clinical trials. In addition, this study demonstrated that infliximab may reduce the overall costs of management of Crohn's disease by limiting associated health care utilization. Results also supported the theory that infliximab acts as a steroid-sparing agent. Further investigation into the impact of infliximab on healthcare usage and the prescription of corticosteroids could be an exciting and challenging field for research in the future.

INTRODUCTION

Crohn's disease is a chronic, relapsing, inflammatory disease of the gastro-intestinal tract. Manifestations of the disease may be severe, and lead to long-term therapy with a variety of medications and/or surgery. There are two main classifications of the disease, including the relapsing-remitting chronic active variety, and the penetrating or fistulising variety. Tumour necrosis factor-alpha (TNF-α) is a pro-inflammatory protein believed to play a major role in the pathogenesis of Crohn's disease (CD). Significantly higher levels of TNF-α have been found in the intestinal mucosa of patients with CD compared with controls. The development of an anti-TNF-α antibody, which inhibits the bioactivity of TNF-α, is a recent and exciting strategy in the treatment of CD.[1] Infliximab, a murine-human chimeric anti-TNF-α proclonal antibody, is one such pharmacological agent. In clinical trials, approximately two-thirds of patients with chronic active CD responded to this therapy, and one-third of patients remained in full clinical remission in the short-term. However, it may not be possible to accurately identify potential responders and non-responders.

Although CD is a severe, debilitating condition, the life expectancy is the same as for the general population.[2] Thus, many patients with CD will require treatment for most of their adult lives. A study performed by Cohen and colleagues elucidated that surgery accounts for the majority of hospitalisations in Crohn's disease, almost 40% of the total cost, and 75% overall charges and reimbursements.[3] Due to the initial high cost of treatment, determining which sub-groups of patients will respond to specific cytokine therapy has important implications for patient management and remains the challenge of the future.

It has been claimed that infliximab (Remicade®, Centocor, Inc., Malvern, PA, USA) has a role as a steroid-sparing agent in luminal Crohn's disease.[4] However, confirmation in clinical settings has proven difficult. A recent study evaluated the impact of infliximab on steroid usage using as "steroid equivalence test," but failed to yield statistically significant results.[5]

MATERIALS AND METHODS

Patients

The Department of Gastroenterology, AMNCH, has treated 46 patients with infliximab over a two and a half-year period, 25 of which were investigated for this study. This group of 46 patients represents the largest single experience with this treatment in Europe outside clinical trials. In 1998, prospective documentation of clinical response, health economic and quality of life data, and blood for serum cytokine analysis was initiated. Patient records were analysed for determination of the health economic impact of treatment, and for investigation of the role of infliximab as a "steroid-sparing" agent. These patients included both males and females, and those experiencing both chronic active and fistulising forms of CD.

Disease Activity

The CDAI (Crohn's Disease Activity Index) is a standard measure of the activity of disease and this proved a useful tool in this study. A score of higher than 150 indicates active disease. Response to infliximab was defined as a reduction in the CDAI either by 70 points or more, or to a score of less than 150.

The Economic Impact of Infliximab

The determination of economic data involved intensive perusal of each patient's medical records. All healthcare usage was recorded for each patient for two years pre- and post-infliximab therapy, and this period of time was divided into eight six-month intervals. For each patient, detailed economic analysis was performed, recording: a) hospital admissions, b) length of stay, c) visits to the A & E department, d) the number of gastrointestinal (GI) surgeries performed, e) the number of courses of IV steroids administered to each patient, f) the number of occasions where TPN was required, and if so, the duration of TPN in days, g) the number of OGDs, or colonoscopies performed, as well as other procedures that involved endoscopy such as ERCP, h) the number of GI x-rays, ultrasounds and CTs etc. performed, i) the number of other (non-GI) procedures performed including other surgical procedures, j) the number of non-GI x-rays, ultrasounds and CTs etc. performed, k) the number of GI clinic visits and l) the number of non-GI clinic visits. This was collated with existing prospective data. The methodology also involved visiting or contacting a number of other hospitals to collect information.

Infliximab's Role as a Steroid-Sparing Agent

In this study, the medical records of all chronic active patients were analysed, noting the dosages and duration of treatments with standard systemic oral steroids (e.g. prednisolone) and the more locally acting, gastrointestinal tract-specific steroids (e.g. budesonide). The years leading up to and following initiation of treatment with infliximab were analysed, and an average daily dosage of both prednisolone and budesonide was calculated for each 6-month period. Finally, the weeks in which prednisolone was not administered were calculated, again in each 6-month period pre- and post-infliximab therapy.

RESULTS

A total of 25 patients were analysed for age, gender, CDAI, sub-type of CD, length of follow-up, smoking status, and response to infliximab (Table 1). There was a 73.1% response to infliximab.

Analysis of Economic Data

Analysis of the economic data yielded interesting results. Table 2 summarises the main components of health-care usage as noted from each patient's medical records. The total usage of health-care facilities was calculated for the period before and after first infusion of infliximab, and the results were compared, with a percentage increase or decrease being noted.

Certain parameters, however, underwent little change. For example, although the number of admissions to hospital decreased

Table 1. Patient Characteristics

Characteristic	
Age, mean ± std. error	34 ± 2.04 years
Gender	73% female
CDAI, mean ± std. error	268.0 ± 24.08
Predominant CD sub-type	69% chronic active
Follow-up, mean ± std. error	20.2 ± 1.64 months
Smokers/ex-smokers	31%/12%
Response to infliximab	73% response

CDAI, Crohn's Disease Activity Index

Table 2. Economic Data

Type of Healthcare Use	Pre-Infliximab	Post-Infliximab	% Increase or Decrease
Hospital admissions (total n)	32	17	47% decrease
Admissions during which IV steroids were employed(%)	43.5%	19.2%	24% decrease
Patients requiring at least one endoscopy (%)	63.5%	27.3%	36% decrease
Patients requiring at least one radiological procedure (%)	63.5%	40.9%	23% decrease
GI clinic visits (total n)	181	207	13% increase

markedly, the mean length of stay remained relatively unchanged, decreasing by 3.6%. Also unremarkable was the percentage change in the number of admissions involving GI surgery, a small increase of 4.6% was noted. Finally, the total number of administrations of TPN (total parenteral nutrition) decreased by 4.3%.

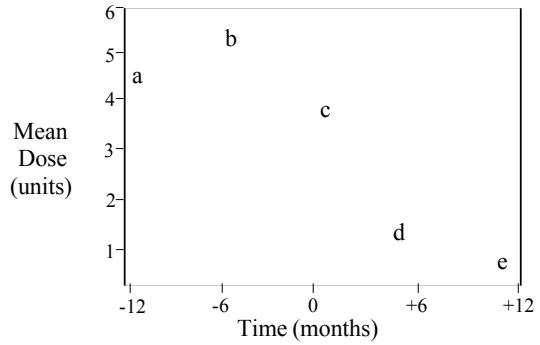

Figure 1. Mean daily dosage of prednisolone: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) the week of treatment, d) 6 months after treatment and e) 12 months after treatment.

Results for the Steroid Data

The results based on the analysis of the steroid data for each patient are shown in Figures 1, 2 and 3. This study found that the mean daily dosage of prednisolone decreased during the 12 months post-infliximab therapy, when compared with the 12 months prior to therapy. Similarly, the mean daily dosage of budesonide decreased in the 12-month period after infliximab therapy (Figs. 1 and 3). Of note, as depicted in Figure 2, the weeks free of prednisolone increased in number after infliximab therapy.

DISCUSSION

The results of anti-TNF-α therapy in clinical trials for patients with CD demonstrate an exciting breakthrough in the medical management of inflammatory bowel disease. In addition, this study found a high response to infliximab, with 73.1% of patients studied being classed as responders. This is higher than the 66.6% of responders noted in clinical

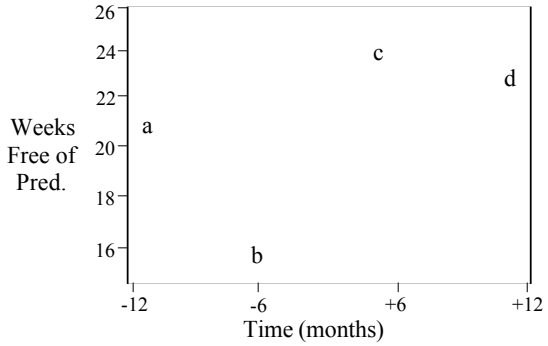

Figure 2. Total number of weeks free of oral corticosteroid prednisolone: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) 6 months after treatment, d) 12 months after treatment.

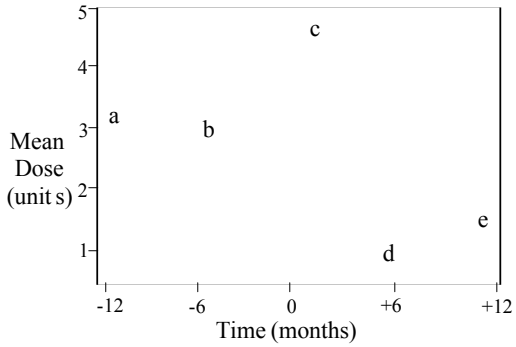

Figure 3. Mean daily dosage of locally-acting oral corticosteroid budesonide: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) week of treatment, d) 6 months after treatment, and e) 12 months after treatment.

trials. Possible reasons for this difference could be that the sub-group analysed in this report may not have included some of the patients with a more resistant or complicated disease. The majority of the patients had a very active disease, as shown by the mean CDAI, 267.97 ± SE 24.08. Indeed, the maximum value for CDAI in the subgroup of patients was 514.8. It is interesting to note that 42.3% of patients were either current smokers or had a history of smoking, as smoking has previously been implicated in the pathogenesis of Crohn's disease.

Medical economics since the 1990s has concentrated on the delivery of quality medical care to all patients while trying to minimise costs.[6] The Hay and Hay analysis of 1992 calculated that hospitalisation and surgery accounted for most of the annual medical costs associated with CD.[7] One might therefore conclude that any treatment that reduces the number of surgical hospitalisations should decrease both the cost of Crohn's disease admissions and the overall costs. Infliximab is an expensive medication, (over £1200 IR per infusion of the medication) thus, its impact on health-care usage has major implications. Thus, the findings of this study are exciting, in that, after infliximab therapy, the number of admissions to hospital decreased markedly, by 46.9%. It is interesting to note that the number of procedures such as radiological investigations and endoscopies also decreased; perhaps each patient's symptomatic improvement after infusion of infliximab reduced the need for performing investigations. Of note, surgical procedures increased in frequency post-infliximab, as did GI clinic visits. Indeed, surgery is the final option in many patients who fail to respond to infliximab. It would be stimulating to further analyse the economic data, perhaps subdividing it into patients who responded to treatment and those who did not.

Steroids are commonly employed in the treatment of acute flare-ups of chronic active disease. Although they are effective, they are associated with problems, such as the development of steroid-dependent or steroid-resistant disease, and the prevalence of unpleasant side effects including: truncal obesity, easy bruising, gastro-intestinal upset, moon-shaped facies, striae and even psychotic episodes. A particularly sinister side effect of steroids is the increased risk of developing osteoporosis in later life. Thus, any treatment that reduces the prescription of corticosteroids will enhance their efficacy in future use and decrease the incidence of severe side-effects. As depicted in Figures 1 and 3, the mean daily dosages of prednisolone and budesonide increased immediately prior to treatment with infliximab, indicating the development of active disease. Subsequent to therapy with infliximab, the mean daily dosage decreased. This would support the postulate that infliximab has a "steroid-sparing" role. Figure 2 almost mirrors these results, as the mean number of weeks free of standard oral steroids (prednisolone) increases post-infliximab.

CONCLUSION

The findings from this study of 25 patients with chronic active CD are comparable to those previously achieved in the controlled setting of clinical trials. Infliximab has been shown to reduce the overall use of health care, especially the total number of admissions to hospital. This suggests that infliximab therapy, although expensive, may actually reduce the overall cost of Crohn's disease. In addition, subsequent to treatment with infliximab, corticosteroids in general were prescribed less, thus supporting the theory that infliximab acts as a steroid-sparing agent. Further investigation into the impact of infliximab on health-care usage and the prescription of corticosteroids could be an exciting and challenging field for research in the future.

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Survey of Attitudes Toward Rapid HIV Testing and Current HIV Testing Procedures Among Patients in Baltimore (USA) STD Clinic

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ABSTRACT

Objectives: A survey-interview of 126 patients at the STD clinic in Baltimore, Maryland, USA was conducted to determine the patients' perception and feelings toward existing HIV procedures as compared to rapid HIV testing. Rapid HIV testing can be performed in less than fifteen minutes, as opposed to the traditional time-consuming ELISA test that takes 3.5 to 4 hours. **Methods:** Study subjects were between 14 and 68 years of age and were all patients of the STD clinic. The questionnaire surveyed patients' experiences with HIV counseling, reasons for getting tested, perceptions of HIV risk and feelings toward rapid HIV testing. **Results:** 33.3% of the patients had previously failed to return for HIV test results. A significant number of the patients cited inconvenience as the most significant factor in not retrieving test results. Most said that they would prefer rapid HIV testing. Sixty nine percent of the patients claimed that they never received any type of pre-test counselling. However, among the patients who received some type of counseling at the Baltimore STD clinic, 58.3% rated the session favourably as 5 out of 5. These results suggest that routine HIV counseling should be improved, and that it may be advantageous to introduce rapid HIV testing as an option for HIV testing in STD clinics.

INTRODUCTION

Rapid human immunodeficiency virus (HIV) tests that make results available in less than an hour are currently being developed. Rapid testing would allow both pre-test and post-test counselling to be performed within the same clinic visit. Counselling is an important tool in HIV care as the disease is associated with significant psychological stressors. The availability of rapid HIV testing may influence the patients' reasons for getting tested and perceptions of testing procedures.

The Centers for Disease Control and Prevention (CDC) in Atlanta is now urging healthcare workers to screen patients with rapid HIV tests instead of using the time-consuming enzyme-linked immunosorbent assay (ELISA).[1,2] The CDC's recommendation was based on statistics that many test takers do not return for results. The CDC estimates that as many as 250,000 individuals in the United States are unaware that they are infected with HIV. It has been further estimated that rapid HIV testing may capture as many as 70,000 newly infected people each year.[1,3]

As its name suggests, rapid HIV tests can be performed in less than fifteen minutes, as opposed to the traditional time-consuming ELISA test that takes 3.5 to 4 hours. With the rapid HIV test, a negative result is considered definitive and does not require further testing. Patients can then be alerted of the results and counselling can be initiated within a single clinic visit. Positive rapid tests require confirmatory testing. A person with positive results will be counseled accordingly and referred for HIV treatment.

Rapid HIV tests are believed to be both cost-effective and accurate. They have been shown to reduce costs by 82% compared to ELISA as there is no need for storage and transportation of specimens and for patients to return. In addition, rapid HIV tests demonstrate sensitivity and specificity comparable to ELISA tests (sensitivity > 96% and specificity > 99%). [4]

Rapid HIV tests are intended to promote more frequent testing among at risk populations and allow for more appropriate counseling. Rapid tests are recommended when the advantage of rapid reporting outweighs the potential danger of reporting false-positive results. This applies to pregnant women in labor who have not been tested or whose results are not available. Rapid tests could provide quick test results so that HIV-infected mothers can receive antiretrovirals to prevent vertical transmission.

This study is intended to provide a better understanding of patients' attitudes and motives toward HIV testing, and to highlight potential flaws in current procedures.

PATIENTS AND METHODS

A survey was conducted on 126 patients between 14 and 68 years of age who visited the inner city Sexually Transmitted Disease (STD) clinic in Baltimore, Maryland during June, 2001. Only patients of the STD clinic were allowed to be included in the study. All study participants gave written informed consent. Participants were assured that refusal to participate did not penalize them or have any impact on future care at the STD clinic. All identifiers were removed to ensure patient confidentiality. The study was approved by the participating Institutional Review Board (IRB). The results from the survey were coded and entered into STATA version 7.0 for analysis.

The questionnaire included elements on the patients' experiences of pre-test and post-test HIV counseling, their reasons for getting tested, their perception of their risk to HIV and their feelings about rapid HIV testing. Participants were asked open-ended questions and the answers were recorded by the interviewer in a multiple-choice format.

RESULTS

A total of 126 patients were enrolled in the study. Seventy-three (58%) were male ranging in age from 17 to 68 years, with a mean of 33 years (SD, ±11.6) (Table 1). Fifty-three (42%) were female, ranging in age from 14 to 55 years, with a mean of 29 years (SD, ±10.6). The vast majority of patients, 120 (95%), were of African-American descent.

A total of 55 patients (44%) were tested within the preceding 6 months, while 42 (33%) patients had last been tested more than 12 months previously. Commonly cited reasons for undergoing HIV testing included personal reassurance (n=73, 58%), routine clinical examination (n=37, 29%), pregnancy or release from jail (n=8, 6%), and financial incentive (n=4, 3%) (Table 2). Five patients (4%) did not cite a reason or had not previously been tested. Patients were also asked to rate their perceived risk of contracting HIV, from low (=1) to high (=5) risk. The largest number of patients (n=61, 49%) perceived their risk as low (=1), 20 patients (16%) rated their risk of infection at 2, 12 patients (10%) at 3, 8 patients (6%) at 4, and 23 patients (19%) at the highest risk level, 5. Among the subgroup of patients who cited personal reassurance as a motivation for undergoing testing (n=73), 25 (47%) rated their risk at 1. The majority of patients (n=87, 69%) claimed to having never received counselling as part of their previous HIV testing procedure. This figure includes 24 patients whose HIV testing occurred as part of a routine clinical examination. Twelve patients who did receive HIV-related counselling as part of their routine examination revealed that the content of pre-test counselling included information only on the testing procedures and of risk awareness. Patients who confirmed having received HIV test-related counseling (n=39, 31%) rated their satisfaction of the testing procedures at the Baltimore STD clinic from low (=1) to high (=5). Twenty-two patients (56%) rated their rated their satisfaction at 5, 8 (21%) rated it at 4, 6 (15%) rated it at 3, 1 (3%) rated it at 2, and 2 (5%) rated it at 1.

Sixty-seven percent (81 of 121 tested) of patients who had been tested previously returned for results. Fifty-two of these 81 patients (64%) returned at their scheduled appointment while the remaining 29 patients

Table 1. Patient Demographics (n=126)

Characteristics		n (%)
Sex		
	Male	73 (58%)
	Female	53 (42%)
Age, mean ± SD (range in years)		
	Male	33 ± 11.6 (17-68)
	Female	29 ± 10.6 (14-55)
Race		
	African-American	120 (95%)
	Caucasian	6 (5%)

SD, standard deviation

Table 2. Cited reasons for undergoing HIV testing (n=126)

Reasons	n (%)
Personal assurance	73 (58%)
Routine clinical examination	37 (29%)
Required (due to pregnancy or release from jail)	8 (6%)
Financial incentive	4 (3%)
Not previously tested or no reason cited	5 (4%)

Table 3. Cited reasons for failure to return for HIV test results (n=40)

Reasons	n (%)
Assumed outcome of result	11 (28%)
Inconvenient to return the following week	10 (24%)
Feared results	4 (10%)
Results were insignificant	1 (2%)
No response given or could not recall	14 (36%)

(36%) returned at a later date. Of the patients who returned for results, only 36 (44%) reported to have had counselling at the time of receiving their results. The counselling included specifics on HIV/AIDS, such as an interpretation of what positive or negative results really mean, information on how to keep from getting infected if the test result is negative, and treatment options and ways to prevent transmission of HIV if the result is positive. Of the 40 patients that did not return for their results, 11 (28%) said they assumed the results, ten (24%) claimed it was inconvenient to return, four (10%) failed to return out of fear, one (2%) claimed the test result was insignificant and 14 (36%) were unable to recall why they failed to return for their results (Table 3).

When patients were asked whether they would prefer to know their HIV test results in a few hours rather than waiting one week, 89% wished to know their results in a few hours. Twenty-four percent of the patients who failed to return said it was inconvenient to return to the clinic the following week and preferred the rapid HIV test. Of the 14 patients who preferred the traditional one-week HIV test, 3 answered that they were skeptical of the rapid HIV test and would rather receive results that were reliable. They feared that reliability would be compromised with speed in getting the results. The others commented that they would rather not find out about their results that day for they were not emotionally prepared to receive their results. Eighty-eight percent of the patients who did not return for their results said that they would prefer the rapid HIV rapid test (Table 4). Some commented that they felt anxious waiting around for their test results. Also, it is interesting to note that only 38% of the patients who preferred the traditional HIV test and 32% of those who preferred the rapid HIV test rated themselves as high risk of getting HIV.

Table 4. Summary of preference for rapid HIV test

Population	% Preferring Rapid HIV Test
All Patients (n=126)	89%
Patients who failed to return for results	88%
Patients who failed to return for results due to inconvenience	23%
Patients with high (5 of 5) perceived risk of HIV infection	81%
Patients with 4 of 5 perceived risk of HIV infection	86%
Patients with 3 of 5 perceived risk of HIV infection	91%
Patients with 2 of 5 perceived risk of HIV infection	79%
Patients with low (1 of 5) perceived risk of HIV infection	95%

DISCUSSION

It is important to realize that there may be a multitude of factors that may influence a patient's decision to test for HIV. For example, it may be due to issues around illness or death of friends, guilt, sexual assault, testing for personal assurance when relationships start or end, or when embarking on new financial ventures or planning a pregnancy. The limitation of the study is that the study population was a highly selected group. Since eligibility depended on being a STD clinic patient, the subjects were self-selected. Also, the survey results were purely based on patient interview in that none of the responses were checked against past records for accuracy.

Also, the patients' response on counselling brings light upon the fact that the delivery of counselling in certain clinics can be improved. Most of the patients claimed that they received no form of counselling before the test or at the time of the test results. However, according to Maryland state law, counselling is a mandatory process of HIV testing. This discrepancy may be due to mode effect on the question structure; it may have been due to the patients' impression of "counselling" or the interviewer's error of not clarifying the definition of counseling. Also this may also be due to recall bias, as many patients may have forgotten they received counseling if testing occurred over 6 months previously.

The results suggest that most patients are satisfied with the current testing procedures at the Baltimore STD clinic. However, the significant number of people who failed to return for their test results seems to suggest that rapid

HIV tests may be appropriate. Most patients explained that the reason why they did not return for their results the following week was because of inconvenience and that they would prefer a rapid HIV test. Thus in a clinical settings such as the STD clinic with high HIV prevalence and low percentage of persons returning for results, use of rapid tests may be beneficial. If health care providers choose to use rapid HIV test results to the patients, high quality testing and counseling must be ensured. With rapid testing, skilled staff must be present at all times and prepared to give immediate counseling when the test results are available a few hours later.

It is also important to consider the patients who raised important public health concerns regarding test accuracy and the immediate notification of test results. Hence, people have various preferences for HIV tests. By making multiple types of HIV tests available, people are given options to apply to different situations. Thus, more people will be encouraged to undergo HIV testing resulting in a higher percentage of the population being aware of their serological status. In this way, people will more likely behave responsibly regarding their sexual practices and health.

It is likely that high-risk individuals who are unaware of their HIV serological status may transmit the virus through risky behavior or miss the opportunity to receive early treatment. It is difficult to prevent or control the HIV/AIDS epidemic when people who are infected unknowingly continue to spread the disease or fail to utilize the treatment options for HIV infection. Thus, the first and most important role in fighting the epidemic is to promote HIV testing so that people can receive treatment and referrals soon after their infection to prevent the emergence of opportunistic infections. Also, patients who learn of their positive status can take immediate precautions to prevent transmitting the virus to others.

It is not easy to promote HIV testing. Most people obtain false information about HIV testing or are unaware of the tests. Thus it is the responsibility of the public health practitioners and health care workers to maintain close communication among researchers, policy makers, and the community in order to make informed decisions for the current situation.

It is critical for health care workers to be familiar with the current HIV tests available and their advantages and disadvantages. The sensitivity, specificity, cost-effectiveness, efficiency, and the patient's personal preference must be considered before making a choice.

There are still many questions and problems regarding HIV testing that must still be resolved before any major changes can be made. In the meantime, small steps can be made by individuals by educating them about current HIV tests that are available and encouraging them to be tested.

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Physiological and Metabolic Profiling of Women with Type 2 Diabetes and Former Gestational Diabetes

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) represents a variant of Type 2 diabetes with potential health consequences for both mother and baby. GDM is also a risk factor for the later development of Type 2 diabetes in women. The purpose of this study was to compare the physiologic and metabolic profile of women with Type 2 diabetes with a history of GDM to those without a history of GDM. **Patients and Methods:** A retrospective chart analysis was conducted on 176 female patients, including 28 (16%) with a prior history of GDM. A subgroup of 6 non-GDM and 3 GDM had an insulin modified (0.05 U/kg) intra-venous glucose (0.3 g/kg) tolerance test (IVGTT) to assess insulin sensitivity and first phase insulin secretion. **Results:** In our results, a history of GDM was associated with an earlier onset of diabetes (43.4±12.1 vs. 57.4±11.1 years for the GDM and non-GDM groups respectively, $p<0.001$). Despite having a longer duration of diabetes the lipid profile of the GDM group was similar, as was the HbA1c, body mass index, waist-to-hip ratio and blood pressure. The incidence of dyslipidemia (50% vs. 53% for the GDM and non-GDM groups respectively), hypertension (64.2% vs. 76.4%) and cardiovascular disease (14.3% vs. 29.2%) was similar between groups. Fasting plasma glucose was similar but fasting insulin was higher in the non-GDM group. **Conclusion:** Type 2 diabetes patients with a prior history of GDM have an earlier onset of diabetes. Screening for GDM should be universally performed to identify these patients early, and treatment should be instituted to delay or prevent the progression to Type 2 diabetes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first detected during pregnancy.[1] It represents an important variant of Type 2 diabetes with potential for morbidity for both mother and baby. It is also recognised to be one of the most important risk factors for the later development of Type 2 diabetes in women. It is often symptomatic and therefore likely that women with GDM are not diagnosed. An earlier pilot study in Ireland has shown that about half of all cases of GDM are missed.[2]

At present, the pathogenesis of GDM is not fully understood. A potential mechanism for GDM is the development of insulin resistance during pregnancy in women whose pancreatic insulin secretion is incapable of adequately compensating to maintain normal glucose homeostasis during gestation. Research indicates that defects in the regulation of glucose clearance, glucose production, and plasma free fatty acid concentrations, together with defects in pancreatic beta-cell function, precede the development of Type 2 diabetes mellitus in women with GDM.[3] One study revealed that insulin sensitivity in a group of pregnant women was reduced to 50%.[4] The increment of insulin resistance was compensated by an enhancement of the first phase of insulin secretion, which was increased more than twofold. This research illustrated that pregnancy is a state of physiologic insulin resistance compensated by an increase of insulin secretion.

There is an immediate return of insulin sensitivity post-partum. The glucose metabolism is restored to a completely compensated non-diabetic baseline similar to original levels which prevailed prior to pregnancy. However, subsequent pregnancies or weight gain, or both, increase the risk of progression to Type 2 diabetes in women with a prior history of GDM.[5-9]

Type 2 diabetes in women is a growing public health problem. Women with Type 2 diabetes have a high risk for cardiovascular and other complications, and have a worse prognosis to these complications than non-diabetic women.[10,11] Women with Type 2 diabetes have a higher relative risk of cardiovascular morbidity and mortality than men with Type 2 diabetes. Early identification of diabetes and early institution of interventions to modify risk factors may be ways to prevent long-term complications and improve the outcomes of Type 2 diabetes. At present, Ireland does not routinely screen for GDM.

HYPOTHESIS

Former GDM subjects with current Type 2 diabetes form a distinct sub-phenotype within the diabetes clinic. Based on evidence from other populations, we expect that women with prior history of GDM have different physical and metabolic profiles, and have more severe defects in insulin secretion in proportion to their degree of insulin resistance.

OBJECTIVES

Our survey involved the complete population of female subjects attending the Diabetes clinic at the outpatients department at St. James Hospital for the treatment of Type 2 diabetes. We compared clinical and metabolic characteristics of these women, specifically demographic data, history of GDM, physical characteristics, metabolic characteristics, the presence of DM complications, and medications used by the patients. In a small number of these women, detailed metabolic studies including an OGTT (with measurement of glucose and insulin) and an insulin-modified three-hours intravenous glucose tolerance test (IVGTT) will be performed.

PATIENTS AND METHODS

The study involves the entire female patient population attending the diabetes outpatient clinic at St. James's hospital. All women surveyed were below the age of 82. A few patients with impaired glucose tolerance (IGT) are also included in the study.

The data collected corresponded to patient's history and characteristics found on their chart. If any of the data from the recent appointment were found missing, incomplete or unavailable, then the patient's data from the previous appointment was used. Relevant information was collected and entered into a clinical data sheet specially designed for this study. The data comprises of six areas: demographic data, gestational history, physical characteristics, metabolic characteristics, the presence of DM complications, and medications used by the patients. The figures from the non-GDM patients were compared with those of GDM patients by performing non-paired t-tests.

The demographic data consisted of the age of patient (calculated based on the corresponding age in year 2001), age of diagnosis of DM, duration of DM (correct to year 2001) and family history of DM (whether none, present in first degree relatives or present in second degree relatives).

The gestational history included the patient's parity (the number of pregnancies including miscarriages, live births and still-births) and the presence or absence of GDM.
The physical parameters examined were the patient's height, weight, body mass index or BMI, waist measurement, hip measurement and waist-to-hip ratio. The metabolic characteristics consisted of total cholesterol level, high-density lipoprotein (HDL) level, low-density lipoprotein (LDL) level, triglycerides (TG) level, microalbumin (Malb) level, urinary creatinine (Ur.Cr), microalbumin-to-urinary creatinine (M/C) ratio, glycosylated haemoglobin (HbA1c) and blood pressure (BP) levels.

Insulin modified intravenous glucose tolerance test (IVGTT) was performed in all subjects to determine acute insulin response to glucose (AIRg) as an index of insulin secretion, and to assess the degree of insulin sensitivity by measuring the insulin sensitivity index (Si). The first step of the procedure was cessation of oral hypoglycaemic agents 5 days before the test. The patients then reported to the laboratory 8 am after an overnight fast. Two antecubital intravenous cannulae were inserted, one in each arm. Base line blood samples were obtained for glucose, insulin and C-peptide measurements. A 50% glucose solution (0.3g/kg) was administered intravenously over one minute and blood samples were then obtained at 2-, 4-, 8-, and 19- minutes. At 20-minutes intravenous short acting human insulin (0.05 u/kg, Actrapid, Novo nordisc, Denmark) was administered intravenously over one minute and blood samples continued to be collected at 22-, 30-, 40-, 50-, 70-, 90-, and 180-minutes. Finally, the serum was separated immediately and stored at -20ºC for analysis at a later date.

An oral glucose tolerance test was performed to measure the blood glucose response to a 75 gm oral glucose load. The procedure began with a three-day diet with at least 300 g of carbohydrates per day. Then, after an overnight fast (12 hours), the patients reported to St. James's Hospital at 8 a.m. They had a cannula inserted and fasting blood sample drawn, and then drank 300 ml of a flavoured glucose drink within 5 minutes. Then a blood sample was drawn every 30 minutes for 3 hours.

RESULTS

A total of 176 patients were included in this study. Of these, 148 were patients without prior history of GDM (non-GDM), while the remaining 28 patients were noted to have had prior history of GDM.

There were differences found between the two groups in terms of the age of the

Table 1. Patient Demographic Characteristics

	Non-GDM (n=148)	GDM (n=28)	p-value
Mean age at diagnosis (years, ± SD)	57.4 ± 11.1	43.4 ± 12.1	< 0.001
Mean current age (years, ± SD)	60.7 ± 11.0	50.7 ± 12.0	< 0.001
Mean duration of DM (years)	3.2 ± 3.1	7.3 ± 9.8	< 0.001

patients, the age at diagnosis of Type 2 diabetes mellitus (DM), and the duration of DM in each patient (Table 1). Non-GDM patients were older than GDM patients (61 ± 11.0 vs. 51 ± 12.0 years, $p<0.001$). Non-GDM patients were diagnosed at an older age (57.4 ± 11.1 years) compared to GDM patients (43.4 ± 12.1 years, $p<0.001$). Non-GDM patients demonstrated a shorter duration of DM (3.2 ± 3.1 years) versus GDM patients (7.3 ± 9.8 years, $p<0.001$). Therefore the trend of GDM is that patients present at a younger age and thus have a longer duration of DM.

Family history characteristics revealed a relation to also have Type 2 DM in 53.4% (first- and second-degree relatives) the non-GDM patients and 82.2% of the GDM patients (Table 2). Of these, positive family history in first-degree relatives contributes the major proportion (43.9% of non-GDM patients vs. 67.9% in GDM patients).

There is little difference in the mean parity of both groups (Table 3). When the patients were grouped together with similar parity and then compared, it was found there were differences in the weight and BMI in the group of women who have a parity greater than 4 (mean parity 7.3 ± 2.3), as represented in Table 4.

The weight in non-GDM patients have a mean of 76.2 ± 13.6 kg versus GDM with mean 88.3 ± 14.4 kg ($p=0.02$) (Table 5). The average BMI in non-GDM patients was 29.90 ± 5.10, in contrast with that of GDM patients 35.60 ± 7.50 ($p<0.05$). We conclude that as the women had more pregnancies, the GDM patients will gain more weight and becoming more obese than the non-GDM patients. In general, patients were overweight, with a mean BMI of 32.8 ± 7.0.

The metabolic profiles were similar between the two groups of patients (Table 6). Separate non-paired t-tests were performed by grouping patients into 5 categories of BMI: (1) Lean (BMI 25-30), (2) Overweight (BMI 31-35), (3) Obese (BMI 36-40), (4) Severely Obese (BMI 41-45) and (5) Morbidly Obese (BMI>45) (Table 7). When all the data were compared between the two groups in each BMI

Table 2. Family History

Family History	Non-GDM (n=148) n (%)	GDM (n=28) n (%)
None	64 (43%)	5 (17%)
Positive: 1st degree relatives	65 (43%)	19 (67%)
Positive: 2nd degree relatives	14 (9%)	4 (14%)
Unknown	5 (3%)	0%

Table 3. Gestational History

	Non-GDM (n=148) n (%)	GDM (n=28) n (%)
Parity = 0	9 (6%)	0 (0%)
Parity = 1	10 (7%)	2 (7%)
Parity = 2	17 (11%)	7 (25%)
Parity = 3	12 (8%)	3 (11%)
Parity = 4	16 (11%)	4 (14%)
Parity > 4	43 (29%)	9 (32%)
Unknown	41 (28%)	3 (11%)
Mean Parity	4.3 ± 3.1	4.2 ± 2.7

Table 4. Weight and body mass index (BMI) of patients with parity > 4.

	Non-GD (n=148)	GDM (n=28)
No. of patients with parity>4	43	9
Weight in kg mean ± SD	76.2 ± 13.6	88.3 ± 14.1
BMI	29.9 ± 5.1	35.6 ± 7.5

Table 5. Physical Characteristics

Characteristic	All Patients	Non-GDM	GDM
Height, mean ± SD (m)	1.59 ± 0.06	1.59 ± 0.07	1.60 ± 0.07
Weight, mean ± SD (kg)	81.3 ± 19.1	80.4 ± 18.5	85.8 ± 21.9
BMI, mean	32.8 ± 7.0	32.5 ± 6.3	33.9 ± 8.9
Waist measurement, mean (cm)	99.6 ± 11.8	99.6 ± 10.6	99.7 ± 14.8
Hip measurement, mean (cm)	110.0 ± 12.1	109.6 ± 11.5	110.9 ± 13.9
Waist/hip ratio	0.89 ± 0.05	0.90 ± 0.04	0.88 ± 0.070

Table 6. Metabolic Characteristics

	Non-GDM	GDM
Mean Total Cholesterol (mmol/l)	5.20 ± 1.07	5.04 ± 0.98
Mean HDL (mmol/l)	1.19 ± 0.33	1.19 ± 0.32
Mean LDL (mmol/l)	3.11 ± 0.89	2.99 ± 0.77
Mean Triglycerides (mmol/l)	2.07 ± 1.51	2.01 ± 1.07
Mean Fasting blood glucose (mmol/l)	9.6 ± 3.6	10.8 ± 6.1
Mean HbA1c (mmol/l)	8.1 ± 1.7	8.1 ± 2.3
Mean Microalbumin	22.8 ± 20.6	19.8 ± 25.9
Mean Urinary Creatinine	9.0 ± 5.8	11.3 ± 5.9
Mean Microalbumin/Urinary Creatinine ratio	3.46 ± 3.11	3.45 ± 1.91
Mean Systolic Blood Pressure	153.5 ± 21.8	148.5 ± 21.2
Mean Diastolic Blood Pressure	81.8 ± 13.3	81.9 ± 13.4

Table 7. Characteristics by BMI stratification

	Lean	Overweight	Obese	Severely Obese	Morbidly Obese
No. non-GDM/GDM	9/3	21/5	25/9	20/2	8/6
BMI	23.04 ± 1.76	27.25 ± 1.43	32.11 ± 1.49	37.87 ± 1.57	45.19 ± 4.99
Total Cholesterol	5.09 ± 1.45	5.21 ± 0.85	5.11 ± 1.15	5.24 ± 1.17	5.08 ± 0.79
HDL	1.42 ± 0.51	1.11 ± 0.23	1.14 ± 0.38	1.17 ± 0.25	1.03 ± 0.20
LDL	3.03 ± 1.05	3.17 ± 0.74	2.97 ± 0.98	3.09 ± 0.88	3.03 ± 0.65
TG	1.41 ± 0.93	2.32 ± 1.92	2.40 ± 1.58	2.32 ± 2.09	2.17 ± 0.88
FBG	-	10.9 ± 4.2	10.1 ± 5.3	9.6 ± 4.7	12.0 ± 4.0
HbA1c	8.0 ± 1.1	8.4 ± 2.3	8.7 ± 1.7	7.7 ± 1.5	7.3 ± 1.4
SBP	155.0 ± 26.7	146.8 ± 17.6	151.8 ± 17.8	152.1 ± 19.3	163.5 ± 18.6
DBP	82.6 ± 14.3	75.7 ± 7.3	84.5 ± 13.8	85.1 ± 12.1	89.5 ± 12.0

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure

category, significant differences were found in the lean group. The level HbA1c in the non-GDM group was lower, (7.6 ± 1.0) compared to the GDM patients (9.1 ± 0.6), $p<0.05$. The systolic blood pressure was higher in the non-GDM group than GDM (163.8 ± 24.2 vs. 128.7 ± 13.3), $p<0.05$. Of note, the non-GDM patients were older than the GDM (66.4 ± 8.2 vs. 36.7 ± 4.0 years old), which may be contributory to their higher systolic blood pressure.

Oral glucose tolerance tests (OGTT) were performed in 3 non-GDM and 4 GDM patients. Meanwhile, intravenous glucose tolerance tests (IVGTT) were performed on 6 non-GDM and 3 GDM patients. Fasting plasma glucose was similar (9.7 ± 1.1 mmol/l in the non-GDM group and 10.2 ± 2.8 mmol/l in the GDM group) but fasting insulin was higher in the non-GDM group (17.7 ± 6 U/ml) compared to the GDM group (10.3 ± 3.1 U/ml, $p<0.05$). The following two graphs depict the glucose and insulin responses derived from the IVGTT.

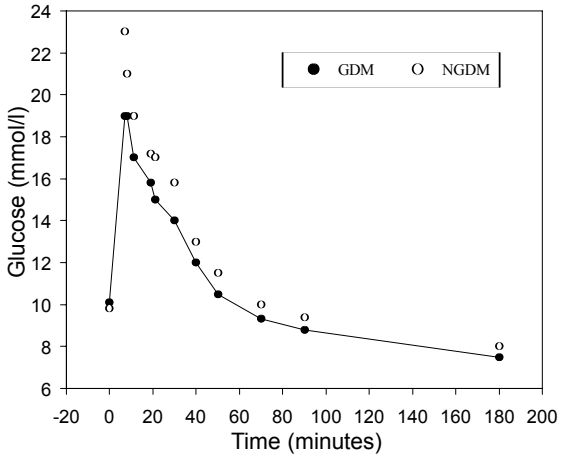

Figure 1. IVGTT Glucose response

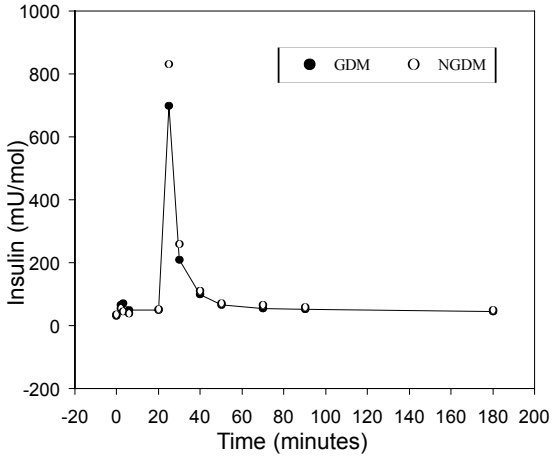

Figure 2. IVGTT Insulin Response

DISCUSSION

From the data analysis we can see that GDM patients tend to present at a younger age and thus have a longer duration of DM compared to the non-GDM patients. Since most patients who had previous history of GDM are at very high risk of developing subsequent DM, every effort should be made to identify them early by screening. The clinicians in Ireland should adopt a universal screening policy on all pregnant women to look for the presence of GDM. A positive history of GDM should alert clinicians that the patient would be prone to develop Type 2 DM in later life and at an earlier age than the general population. These women should have more extensive follow-up by experienced diabetologists after pregnancy; they should be advised to lose weight, exercise regularly and consume healthy diets in hope that these simple, active prevention strategies would prevent or delay the progression to DM. At present, no drug treatment is yet available in preventing the development of DM in non-diabetic women with prior GDM but a research trial has already started in the USA. A randomised, placebo controlled trial of troglitazone is carried out in these women in the hope that chronic administration of this drug may improve insulin sensitivity and reduce the incidence of Type 2 DM.[12] Although the result of this trial is not yet available, it represents an important milestone in pre-emptive treatment of patients with prior history of GDM.

Patients with a history of GDM showed a trend in higher incidence of positive family history, particularly among first-degree relatives. Such a finding may be attributable to an inherited genetic etiology. However, at present, there are still no researches available to identify the genetic causes of GDM.

Overall, the diabetic patients surveyed were mostly overweight, with an average BMI of greater than 30. Parity seems to influence the physical profile of the GDM patients; the more pregnancies they have, the heavier they get and thus attain a greater BMI. As discussed earlier, subsequent pregnancies or weight gain, or both, will increase the rate of progression to the future development of Type 2 diabetes. Therefore, active interventions should target this high-risk group of patients.

The defects in insulin secretion were more pronounced among lean GDM subjects, as evident from a higher level of HbA1c when compared to their counterparts of similar BMI. However, as BMI increases, the physical and metabolic profiles of the GDM patients became similar to those of the non-GDM.

CONCLUSION

This study suggests that GDM patients may be unique in several different aspects. However, more extensive studies on GDM such as molecular, genetic, metabolic, and epidemiological studies are needed to improve our understanding in the characteristics and pathogenesis of GDM. Early identification of GDM status will improve awareness in this subgroup of women and improve preventative strategies including early treatment and follow-up where appropriate.

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