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Tables should be kept to a minimum and be designed to be as simple as possible. Tables are to be typed double-spaced throughout, including headings and footnotes. Each table should be on a separate page, numbered consecutively in Arabic numerals and supplied with a heading and a legend. Tables should be self-explanatory without reference to the text. The details of the methods used in the experiments should preferably be described in the legend instead of in the text. The same data should not be presented in both table and graph form or repeated in the text.

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Abayomi (2000), Agindotan et al. (2003), (Kelebeni, 1983), (Usman and Smith, 1992), (Chege, 1998; 1987a,b; Tijani, 1993,1995), (Kumasi et al., 2001)
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Pitout JDD, Church DL, Gregson DB, Chow BL, McCracken M, Mulvey M, Laupland KB (2007). Molecular epidemiology of CTXM-producing Escherichia coli in the Calgary Health Region: emergence of CTX-M-15-producing isolates. Antimicrob. Agents Chemother. 51: 1281-1286.

Pelczar JR, Harley JP, Klein DA (1993). Microbiology: Concepts and Applications. McGraw-Hill Inc., New York, pp. 591-603.

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Review

The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus

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The aim of this paper is to review the information on type 1 and type 2 diabetes with emphasis on its etiology, pathogenesis and pathophysiology via literature review. Diabetes is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Type 1 diabetes is the result of an autoimmune reaction to proteins of the islets cells of the pancreas while type 2 diabetes is caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, overeating, lack of exercise and stress, as well as aging. The pathogenesis of selective β-cell destruction within the islet in type 1 diabetes mellitus is difficult to follow due to marked heterogeneity of the pancreatic lesions. At the onset of overt hyperglycemia, a mixture of pseudoatrophic islets with cells producing glycogen, somatostatin and pancreatic polypeptide, normal islets and islets containing both β-cells and infiltrating lymphocytes and monocytes may be seen. The autoimmune destruction of pancreatic β cells leads to a deficiency of insulin secretion that leads to the metabolic derangements associated with type 1 diabetes. The main pathophysiological features of type 2 diabetes are impaired insulin secretion and increased insulin resistance. The impairment of pancreatic β cell function notably shows progression overtime in type 2 diabetes although aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc are independent risk factors of pathogenesis of type 2 diabetes mellitus.

Key words: Diabetes Mellitus, Pathophysiology, Pathogenesis, Etiology.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Permanent neonatal diabetes is caused by glucokinase deficiency, and is an inborn error of the glucose-insulin signaling pathway (Njolstad *et al*., 2003). The prevalence of diabetes is increasing rapidly worldwide and the World Health Organization (2003) has predicted that by 2030 the number of adults with diabetes would have almost doubled worldwide, from 177 million in 2000 to 370 million. Experts project that the incidence of diabetes is set to soar by 64% by 2025, meaning that a

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Table 1. Some causes of insulin resistance.

S/No.	Causes
1	Obesity/overweight (especially excess visceral adiposity)
2	Excess glucorticoids (cushing's syndrome or steroid therapy)
3	Excess growth hormone (acromegaly)
4	Pregnancy, gestational diabetes
5	Polycystic ovary disease
6	Lipodystrophy (acquired or genetic, associated with lipid accumulation in liver)
7	Autoantibodies to the insulin receptor
8	Mutations of insulin receptor
9	Mutations of the peroxisome proliferators' activator receptor γ (PPAR γ)
10	Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
11	Hemochromatosis (a hereditary disease that causes tissue iron accumulation).

Source: Guyton and Hall (2006).

Table 2. Clinical characteristics of patients with Type 1 and Type 2 diabetes mellitus.

Features	Type 1	Type 2
Age of onset	Usually less than 20 years	Usually greater than 30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

Source: Guyton and Hall (2006).

staggering 53.1 million citizens will be affected by the disease (Rowley and Bezold, 2012). The estimated worldwide prevalence of diabetes among adults in 2010 was 285 million (6.4%) and this value is predicted to rise to around 439 million (7.7%) by 2030 (Shaw et al., 2010). There are two main types of diabetes mellitus: i. Type 1 diabetes, also called insulin dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion by beta cells of the pancreas.

ii. Type 2 diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin.

The reduced sensitivity to insulin is often called insulin resistance and its causes are shown in Table 1. In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain (Guyton and Hall, 2006). As a result of this, blood glucose concentration increases, cell utilization of glucose falls increasingly lower and utilization of fats and proteins increases. The clinical characteristics of patients with type 1 and type 2 diabetes mellitus are shown in Table 2.

EPIDEMIOLOGY AND ETIOLOGY OF TYPE 1 DIABETES (IDDM)

Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide (American Diabetes Association, 2001).

Although type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood (Blood et al., 1975). The incidence of type 1 diabetes is rising. Across Europe, the average annual increase in the incidence in children under 15 years is 3.4% (EURODIAB

ACE study Group, 2000), with the steepest rise in those under 5 years old (Karvonen et al., 1999). Type 1 diabetes is the result of an autoimmune reaction to proteins of the islets cells of the pancreas (Holt, 2004). There is a strong association between IDDM and other endocrine autoimmunity (for example, Addison disease) and an increased incidence of autoimmune diseases are seen in family members of IDDM patients. The three types of autoantibodies known are:

i) Islet cell cytoplasmic antibodies (ICCA): The primary antibodies found in 90% of type 1 diabetics are against islet cell cytoplasmic proteins. The presence of ICCA is a highly accurate predictor of future development of IDDM.

ii) Islet cell surface antibodies (ICSA): Autoantibodies directed against islets cell surface antigens (ICSA) have also been described in as many as 80% of type 1 diabetics. Some patients with type 2 diabetes have been identified, which are ICSA positive.

iii). Specific antigenic targets of islet cells: Antibodies to glutamic acid decarboxylase (GAD) have been identified in over 80% of patients newly diagnosed with IDDM. Anti GAD antibodies decline over time in type 1 diabetics. The presence of anti GAD antibodies is a strong predictor of the future development of IDDM in high risk populations. Anti insulin antibodies (IAAs) have been identified in IDDM patients and in relatives at risk to developing IDDM. These IAAs are detectable even before the onset of insulin therapy in type 1 diabetics. IAA is detectable in around 40% of young children with IDDM (Raju and Raju, 2010).

Pathogenesis of type 1 diabetes mellitus

Type 1 diabetes mellitus is a chronic autoimmune disease associated with selective destruction of insulin-producing pancreatic β-cells (Figure 1). The onset of clinical disease represents the end stage of β-cell destruction leading to type 1 diabetes mellitus. Al Homsi and Lukic (1992) explained that several features characterize type 1 diabetes mellitus as an autoimmune disease:

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);
3. Presence of islet cell specific autoantibodies;
4. Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment;
5. The involvement of monokines and TH1 cells producing interleukins in the disease process;
6. Response to immunotherapy and;
7. Frequent occurrence of other organ specific autoimmune diseases in affected individuals or in their family members.

The pathogenesis of selective β-cell destruction within the islet in type 1 DM is difficult to follow due to marked heterogeneity of the pancreatic lesions. At the onset of overt hyperglycemia, a mixture of pseudoatrophic islets with cells producing glycogen (a cells), somatostatin (d cells) and pancreatic poly-peptide (PP cells), normal islets, and islets containing both b-cells and infiltrating lymphocytes and monocytes may be seen (Al-Homsi and Lukic, 1992). Lymphocytic infiltration is found only in the islet containing residual β-cells and is likely that the chronicity with which type 1 DM develops reflects this heterogeneity of islet lesions (Al-Homsi and Lukic, 1992). In contrast to this chronicity in the natural history of the disease, β-cells are rapidly destroyed when pancreas is transplanted from identical twin donors into their long term diabetic twin mates in the absence of immunosuppression. In these cases, massive insulitis develops rapidly with infiltrating T lympocytes indicating an anamnestic autoimmune reaction (Al Homsi and Lukic, 1992). In addition, this observation also indicates that the chronic time course in type 1 DM (but not in a transplanted pancreas) is a consequence of down regulatory phenomena taking part in immunopatho-genesis of the disease (Al Homsi and Lukic, 1992). Activation of islet antigen - specific CD4+ T cells appear to be absolute prerequisite for the development of diabetes in all animal models of type 1 DM (Gill and Haskins, 1993). CD4+ islet specific T-cell clones derived from diabetic NOD mice, when injected into prediabetic or non diabetes prone Fl mice, induce insulitis and diabetes. It was also reported that CD4+ T cells are sufficient to induce insulitis while CD8+ T cells contribute to the severity of the damage (Yagi et al., 1992). These findings together with the evidence that insulitis in chronic graft versus host disease may occur in the absence of CD8+ T cells suggest that CD4+ T cells may be the only immunocompetent cells required in the disease process. However, it seems that only one subset of CD4+ T cells are responsible for disease induction.

CD4+ T cell bearing alloantigen RT6 are absent in diabetes prone BB rats and appear to protect AO rats from MLD-STZ induced diabetes (Greineh et al., 1987). Down-regulation of diabetogenic autoimmune response by the spleen cells derived from animals treated with adjuvants could also be explained by CD4+ T cell subsets interplay (Ulaeto et al., 1992). High level of THI type cytokines IL-2 and interferon g are found to correlate or/and to enhance induction of autoimmune diabetes in experimental models (Fowell et al., 1991; Campbell et al., 1991). The TH-1 type cells, and in particular their product IFN-g, activate macrophages. In animal, models of type 1 DM electron microscopic studies of pancreata showed

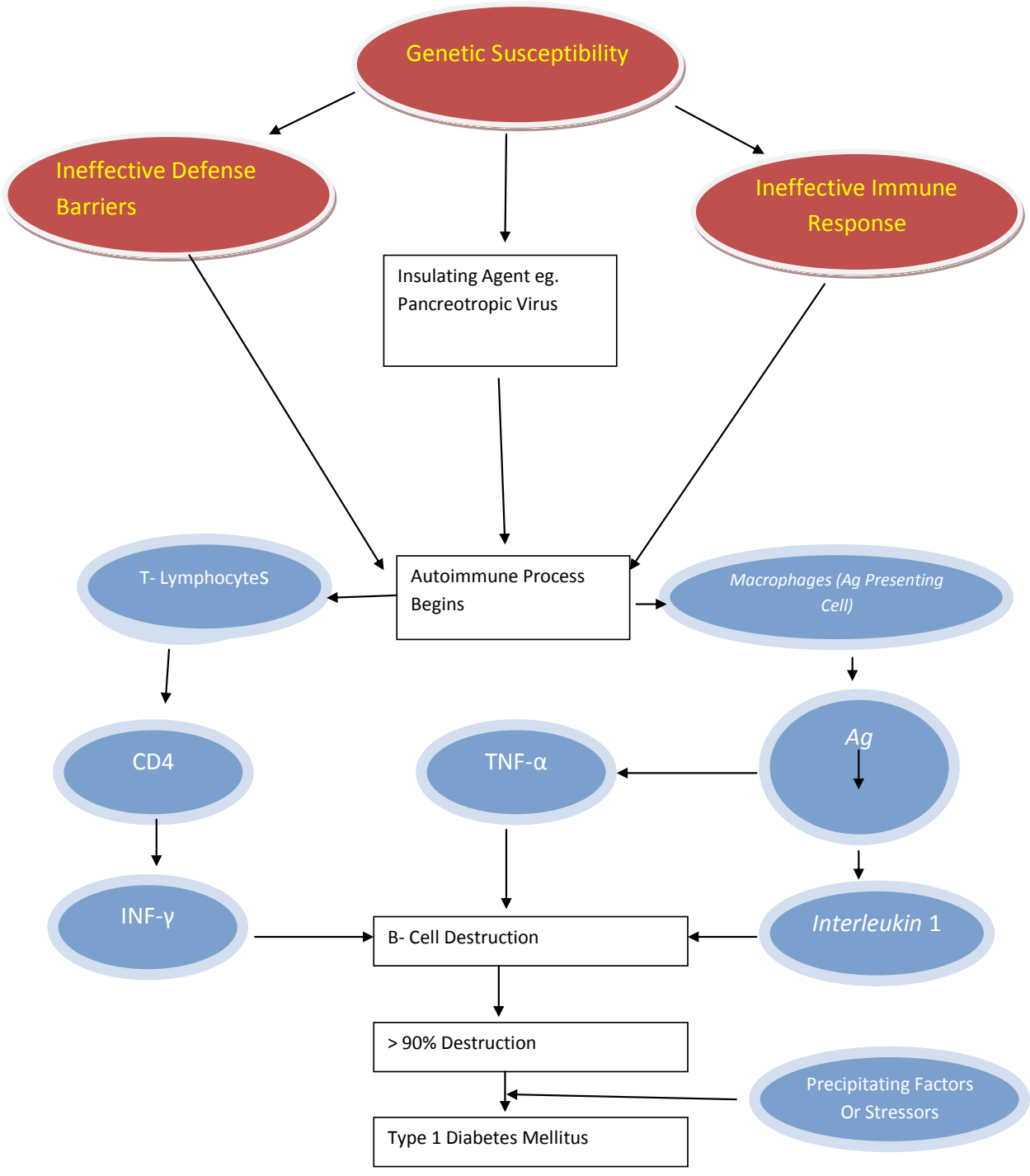

Figure 1. Pathogenesis of type 1 diabetes mellitus.

that macrophages are the first cell type invading the islets(Kolb-Bachofen et al., 1988). *In vitro* studies and studies on perfused pancreas suggest that Interleukin 1 (IL-1) and tumor necrosis factor (TNFa), two cytokines mainly produced by macrophages, induce structural changes of β-cells and suppression of their insulin releasing capacity (Mandrup-Poulsen et al., 1987). However, it seems that IL-1 and TNF do not contribute

appreciably to the cytotoxic activity of macrophages (Kroncke et al., 1991). Interferon g is also a powerful activator of macrophages for nitric oxide synthesis. Recently, evidence has been provided indicating that NO synthase activity is involved in diabetes development (Lukic et al., 1991). These data indicated, for the first time, that nitric oxide may be a pathogenic factor in autoimmunity and suggested a possibility that a new class of immunopharmacological agents, capable of modulating nitric oxide secretion may be tested in the prevention of type 1 DM development (Kolb and Kolb-Bachofen, 1992).

Pathophysiology of type 1 diabetes (IDDM)

The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, the function of pancreatic α-cells is also abnormal and there is excessive secretion of glucagons in IDDM patients. Normally, hyperglycemia leads to reduced glucagons secretion, however, in patients with IDDM, glucagons secretion is not suppressed by hyperglycemia (Raju and Raju, 2010). The resultant inappropriately elevated glucagons levels exacerbate the metabolic defects due to insulin deficiency. The most pronounced example of this metabolic disruption is that patients with IDDM rapidly develop diabetic ketoacidosis in the absence of insulin administration. Although insulin deficiency is the primary defect in IDDM, there is also a defect in the administration of insulin. There are multiple biochemical mechanisms that account for impairment of tissue's response to insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle (Raju and Raju, 2010). This impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue. Raju and Raju (2010) explained that the major metabolic derangements, which result from insulin deficiency in IDDM are impaired glucose, lipid and protein metabolism which are explained in details as follows:

Effects on glucose metabolism

Uncontrolled IDDM leads to increased hepatic glucose output. First, liver glycogen stores are mobilized then hepatic gluconeogenesis is used to produce glucose. Insulin deficiency also impairs non hepatic tissue utilization of glucose. In particular in adipose tissue and skeletal muscle, insulin stimulates glucose uptake. This is accomplished by insulin mediated movement of glucose transporters proteins to the plasma membrane of these tissues. Reduced glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolism. In addition, the level of hepatic glucokinase is regulated by insulin. Therefore, a reduced rate of glucose phosphorrylation in hepatocytes leads to increased delivery to the blood. Other enzymes involved in anabolic metabolic metabolism of glucose are affected by insulin.

The combination of increased hepatic glucose production and reduced peripheral tissues metabolism leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is surpressed, glucosuria ensues. Glucose is an osmotic diuretic and an increase in renal loss of glucose is accompanied by loss of water and electrolyte. The result of the loss of water (and overall volume) leads to the activation of the thirst mechanism (polydipsia). The negative caloric balance, which results from the glucosuria and tissue catabolism leads to an increase in appetite and food intake that is polyphagia (Raju and Raju, 2010).

Effect on lipid metabolism

One major role of insulin is to stimulate the storage of food energy in the form of glycogen in hepatocytes and skeletal muscle, following the consumption of a meal. In addition, insulin stimulates hepatocytes to synthesize and store triglycerides in adipose tissue. In uncontrolled IDDM there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. The free fatty acids are taken up by numerous tissue (except the brain) and metabolized to provide energy. In the absence of insulin, malonyl COA levels fall, and transport of fatty acyl-COA into the mitochondria increases. Mitochondrial oxidation of fatty acids generates acetyl COA that can be further oxidized in the TCA cycle. However, in heaptocytes the majority of the acetyl COA is not oxidized by the TCA cycle but is metabolized into the ketone bodies (acetoacetate and b-hydroxybutyrate). These ketone bodies are used for energy production by the brain, heart and skeletal muscle. In IDDM, the increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose, furthering the ensuing hyperglycaemia. Production of ketone bodies in excess of the body's ability to utilize them leads to ketoacidosis. A spontaneous breakdown product of acetoacetate is the acetone that is exhaled by the lungs, which gives a distinctive odor to the breath. Normally, plasma triglycerides are acted upon by lipoprotein lipase (LPL) that requires insulin. LPL is a membrane bound enzyme on the surface of the endothelial cells lining the vessels,

which allows fatty acids to be taken from circulating triglycerides for storage in adipocytes (Raju and Raju, 2010). The absence of insulin results in hypertriglyceridemia.

Effects on protein

Insulin regulates the synthesis of many genes, either positively or negatively, which affect overall metabolism. Insulin has an overall effect on protein metabolism, increasing the rate of protein synthesis and decreasing the rate of protein degradation. Thus insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concentration of amino acids in plasma (Raju and Raju, 2010). Glucogenic amino acids serve as precursors for hepatic and renal glyconeogenesis, which further contributes to the hyperglycaemia seen in IDDM.

EPIDEMIOLOGY AND ETIOLOGY OF TYPE 2 DIABETES (NIDDM)

Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus (Gonzalez et al., 2009). The rise in prevalence is predicted to be much greater in developing than in developed countries (69 versus 20%) (Shaw et al., 2010). In developing countries, people aged 40 to 60 years (that is, working age) are affected most, compared with those older than 60 years in developed countries (Shaw et al., 2010). This increase in type 2 diabetes is inextricably linked to changes towards a Western lifestyle (high diet with reduced physical activity) in developing countries and the rise in prevalence of overweight and obesity (Chan et al., 2009; Colagiuri, 2010). There are approximately 1.4 million people with diagnosed type 2 diabetes in the UK (Bennett et al., 1995). The incidence of diabetes increases with age, with most cases being diagnosed after the age of 40 years. This equates to a lifetime risk of developing diabetes of 1 in 10 (Neil et al., 1987). Type 2 diabetes is a heterogenous disorder caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging (Kaku, 2010). It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents (Holt, 2004). Type 2 diabetes is the common form of idiopathic diabetes and is characterized by a lack of the need for insulin to prevent ketoacidosis. It is not an autoimmune disorder and the susceptible genes that predispose to NIDDM have not been identified in most patients. This could be due to the heterogeneity of the genes responsible for the susceptibility to NIDDM.

Pathogenesis of type 2 diabetes

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in liver) and insulin secretion (DeFronzo, 1988). In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance (Holt, 2004). Type 2 diabetes mellitus has a greater genetic association than type 1 DM, the pathogenesis of type 2 diabetes mellitus is characterized by impaired insulin secretion and insulin resistance as shown in Figure 2. The 100% concordance rate in identical twins is thought to be over-estimated, due to a selection or reporting bias. A population based twin study in Finland has shown a concordance rate of 40%, and environmental effect may be a possible reason for the higher concordance rate for type 2 diabetes mellitus than for type 1 diabetes mellitus (Kaprio et al., 1992). Type 2 diabetes mellitus affects 1 to 2% of caucasians (Cook et al., 1993) but it is much higher in some ethnic groups such as Pima Indians (Knowler et al., 1990) and Arabs (Richens et al., 1988) and approaches 50% in South India. This indicates that genetic factors are more important than environmental factors. Except for maturity onset diabetes of the young (MODY), the mode of inheritance for type 2 diabetes mellitus is unclear. MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. Glucokinase is a key enzyme of glucose metabolism in beta cells and the liver (Froguel et al., 1993; Hattersley et al., 1992). MODY is defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies (ICA) are negative and HLA-DR3 and DR4 are heterozygous. MODY is rare in Caucasians, less than 1%, and more common in blacks and Indians, more than 10% of diabetics. Chronic complications in MODY were thought to be uncommon but later were found to be more common, indicating its heterogeneity.

Considering MODY as a separate entity may masquerade its association with specific genetic diseases; and without a definite genetic marker, it should be treated as type 1 DM (Tattershall, 1991). Identification of a nonsense mutation in the glucokinase gene and its linkage with MODY was reported for the first time in a French family, implicating a mutation in a gene involved in glucose metabolism in the pathogenesis of type 2

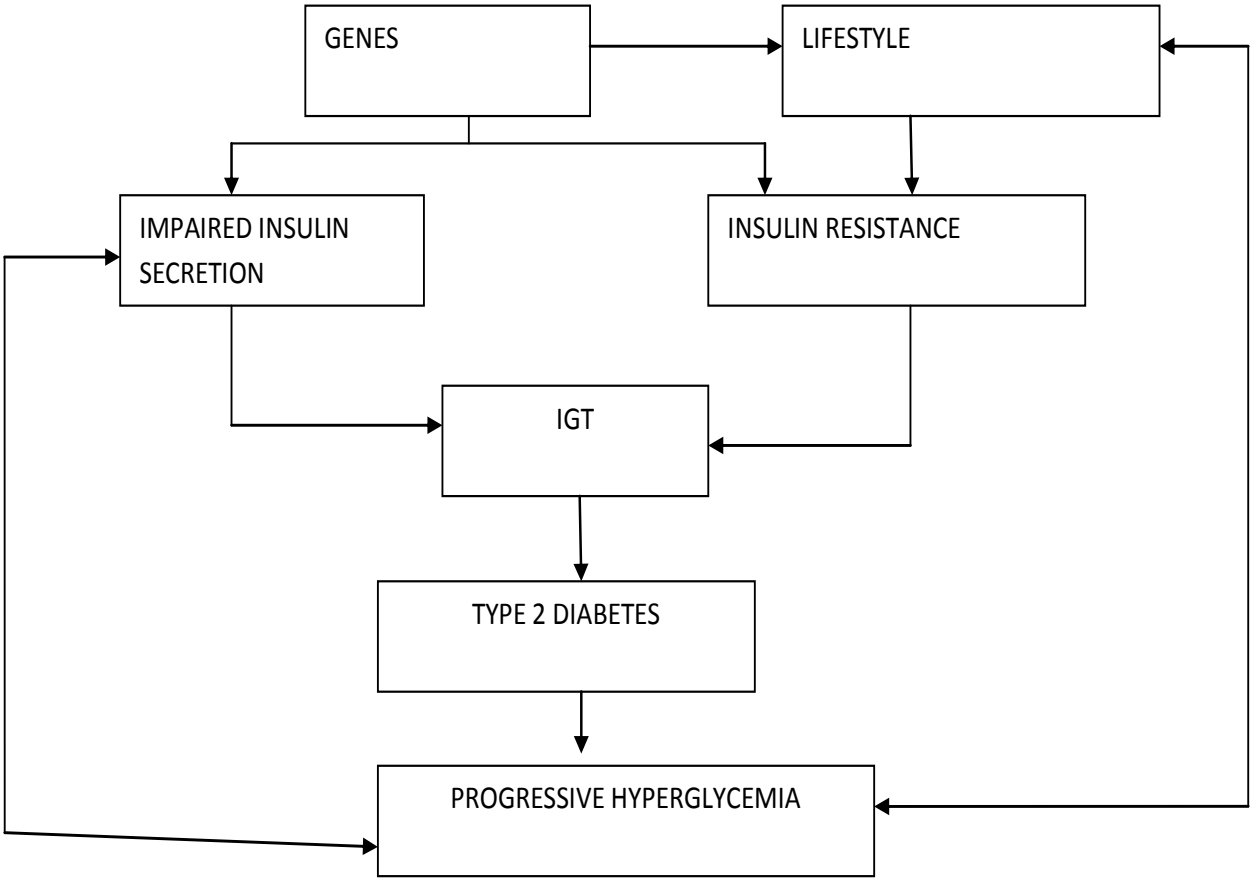

Figure 2. Pathogenesis of type 2 diabetes characterized by impaired insulin secretion and insulin resistance

diabetes mellitus (Vionnet et al., 1992). Later, sixteen mutations were identified in 18 MODY families. They included 10 mutations that resulted in an amino acid substitution, 3 that resulted in the synthesis of truncated protein, and 3 that affected RNA processing. Hyperglycemia in these families was usually mild and began in childhood, whereas the hyperglycemia of MODY families without glucokinase mutations usually appearedafter puberty (Froguel et al., 1993). Molecular genetic studies in type 2 diabetes mellitus, with the exception of MODY, have not been as successful as in type 1 diabetes mellitus. Mutations in the insulin gene lead to the synthesis and secretion of abnormal gene products, leading to what are called insulinopathies (Gabbay, 1980). Most of the patients with insulinopathies have hyperinsulinemia, inherited in autosomal fashion, heterozygous for normal and mutant alleles, and normally respond to exogenous insulin administration. Al Homsi and Lukic (1992) explained that most insulin gene mutations lead to:

(a) Abnormal insulins - Such as insulins Chicago and Wakayama where the mutation leads to an amino acid replacement at an important site for receptor interaction; or

(b) The mutation may interfere in the proinsulin processing to insulin (Chan et al., 1987).

The association of the polymorphic (hypervariable) 5' flanking region of the human insulin gene and type 2 diabetes mellitus is lacking in some population groups, indicating that it may be one of many factors in a multifactorial disease. Even MODY patients have shown no association with this region. It was mentioned earlier that there is a strong association between HLA-DR3/4 and type 1 diabetes mellitus. It was also reported that such an association is present with type 2 diabetes mellitus, rendering HLA-DR3/4 markers for beta cell destruction in these patients (Richens et al., 1988; Tattershall, 1991). Pancreatic abnormalities in islet secretory cells in type 2 diabetes mellitus are noted in beta, alpha and delta cells of the islets. Defects involving insulin secretion include relative decrease in basal

secretion, decreased first and second phases of insulin response, glucose insensitivity and amino acid hypersensitivity of insulin release. The number and volume of beta cells are usually decreased to half the normal, and the alpha cell mass is increased leading to hyperglucagonemia. The islets exhibit hyalinization and amyloid deposition, containing islet amyloid polypeptide (IAPP) or amylin. This is a minor secretory peptide of the beta cells released along with insulin and C-peptide, but its role in the pathogenesis of type 2 DM is not well understood (Steiner et al., 1991). This amylin is thought to produce insulin resistance (Molina et al., 1990). IAAP is reduced with progression of type 2 DM (Enoki et al., 1992). Intimate contact between beta cells and amyloid deposit in type 2 DM is noted by electron microscopy (Westermark, 1973). Away from the islets in the exocrine pancreas, fatty infiltration and diffuse fibrosis are evident. Defective islet cell function is the primary event which may be due to an autoimmune reaction producing hyperglycemia in type 2 DM (Zawala et al., 1992). The insulin receptor gene is located on chromosome 19 and it encodes a protein having alpha and beta subunits including the transmembrane domain and the tyrosine kinase domain (Kahu and White, 1988). Mutations affecting the insulin receptor gene have been identified and their association with type 2 diabetes mellitus and type A insulin resistance is recognized.

Type A insulin resistance is hereditary and type B is an autoimmune disorder (Levy and Hug, 1993). Restriction fragment length polymorphism (RFLP) analysis of the insulin receptor gene (Ohagi et al., 1992), erythrocyte glucose transporter gene, and HLA genes, were not found useful as genetic markers for type 2 DM. Insulin resistance is insufficient to cause overt glucose intolerance, but may play a significant role in cases of obesity where there is known impairment of insulin action. Insulin resistance by itself may be a secondary event in type 2 DM, since it is also found in non-diabetic obese individuals. Insulin secretion defect may be the primary event, presenting as impaired pulsatile secretion of insulin. Hence, hyperglycemia is an inducer as well as a consequence of impaired islet cell function and insulin resistance. Many factors contribute to the insulin insensitivity including obesity and its duration (Evephart et al., 1992), age, lack of exercise, increased dietary fat and decreased fibres and genetic factors.

Fish oil is found to prevent insulin resistance in animals, but not in humans. It has a protective effect against thrombosis and vasospasm in type 2 DM (Mc Veigh et al., 1993). Insulin resistance in type 2 DM is not totally clear, it may involve reduced insulin receptor number, it may be secondary to hyperinsulinemia and hyperglycemia, (Vuorinen-Markkola et al., 1992) or it may result from reduced tyrosine kinase activity (Comi et al., 1987; Bonadonna et al., 1993; Sten-linder et al., 1993) or even abnormalities distal to the receptor involving glucose transporter proteins through a family of glucose transporter genes (Mueckler, 1990). The GLUT2 gene, expressed in liver and pancreatic beta cells, and GLUT4, expressed in skeletal muscle and adipocytes, are strong candidate genes for the genetic susceptibility to type 2 DM. Analysis of these two glucose transporter genes, in addition to GLUT1, encoding for the brain/erythrocyte glucose transporter, has yielded, in Caucasians, no association of any RFLP marker on haplotype with either type 2 DM or obesity (Oelbaum, 1992).

Obesity has genetic as well as environmental causes. It has a strong effect on the development of type 2 DM (Bjorntorp, 1992; Haffner et al., 1992) as it is found in Western countries (NDDG, 1979; Wilson et al., 1981) and some ethnic groups such as Pima Indians (Joffe et al., 1992; Knowler et al., 1993). Obesity is more than just a risk factor; it has a causal effect in the development of type 2 DM against a genetic background. The evolution from obesity to type DM results from a succession of pathophysiological events:

(a) Augmentation of the adipose tissue mass, leading to increased lipid oxidation;
(b) Insulin resistance noted early in obesity, revealed by euglycemic clamp, as a resistance to insulin mediated glucose storage and oxidation, blocking the function of the glycogen cycle;
(c) Despite maintained insulin secretion, unused glycogen prevents further glucose storage leading to type 2 DM;
(d) Complete b-cell exhaustion appears later (Felber, 1992).

Type 2 DM patients have a characteristic shoulder, girdle-truncal obesity. Nutrient composition has also been found to be a risk factor for developing type 2 DM, where increased fat and decreased carbohydrate consumption have contributed to hyperinsulinemia of obesity. Dietary fibres, both soluble and insoluble, improve type 2 DM. It is also found that simple sugars do not directly cause diabetes. Deficiency of micronutrients, such as chromium and copper, is found to be an important cause of type 2 DM in a minority of cases. Stress has also been thought to induce type 2 DM. Actually, obesity and over-availability of food rather than stress are the contributing factors to type 2 DM. Therefore, when permanent change in dietary habits is established, some people should be allowed to escape the "life-long" diagnosis of type 2 DM (Akinmokun et al., 1992).

Environmental factors in the pathogenesis type 2 diabetes

Aging, obesity, insufficient energy consumption, alcohol

Table 3. Factors causing increase in visceral fat.

S/No.	Factors
1	Stress- Related Factors
A	Overeating, especially excessive intake of simple sugars
B	Smoking
C	Increase in alcohol intake
D	Disorders of nervous and endocrine systems: increase in cortisol, abnormality in sex hormone secretion
2	lowered energy consumption due to a lack of exercise
3	Genetic factors
4	Aging

Source: Kaku (2010).

drinking, smoking, etc are independent risk factors of pathogenesis of type 2 diabetes. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance, and is closely associated with the rapid increase in the number of middle and high aged patients. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. Even mild obesity (Body mass index (BMI) < 25) causes a 4 to 5 fold increase in risk of developing diabetes, if accompanied by the increase in visceral fat mass. People prone to visceral fat accumulation due to hyperalimentation, and risk factors for diabetes are linked to the accumulation of visceral fat and the factors causing visceral fats are shown in Table 3.

Pathophysiology of type 2 diabetes (NIDDM)

Individuals with NIDDM have detectable levels of circulating insulin, unlike patients with IDDM and the pathophysiology of type 2 diabetes is described in Figure 3. On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups:

i) Those with normal glucose tolerance.
ii) Chemical diabetes (called impaired glucose tolerance).
iii) Diabetes with minimal fasting hyperglycemia (fasting plasma glucose less than 140 mg/dl).
iv) Diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl).

The individuals with impaired glucose tolerance have hyperglycemia inspite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average NIDDM patients (Holt, 2004). Insulin resistance is the primary cause of NIDDM, however some researcher contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM (Raju and Raju, 2010). Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes (Raju and Raju, 2010). Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferators-activated receptor g (PPARg). PPARg is also a transcription factor and when activated, binds to another transcription factor known as the retinoid x receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPARg is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPARg is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells (Raju and Raju, 2010).

CONCLUSION

The global burden of diabetes is increasing worldwide as it is a costly disease for developing economies of the world. To reduce the pandemic of type 1 and type 2 diabetes and its effects on lives and economies

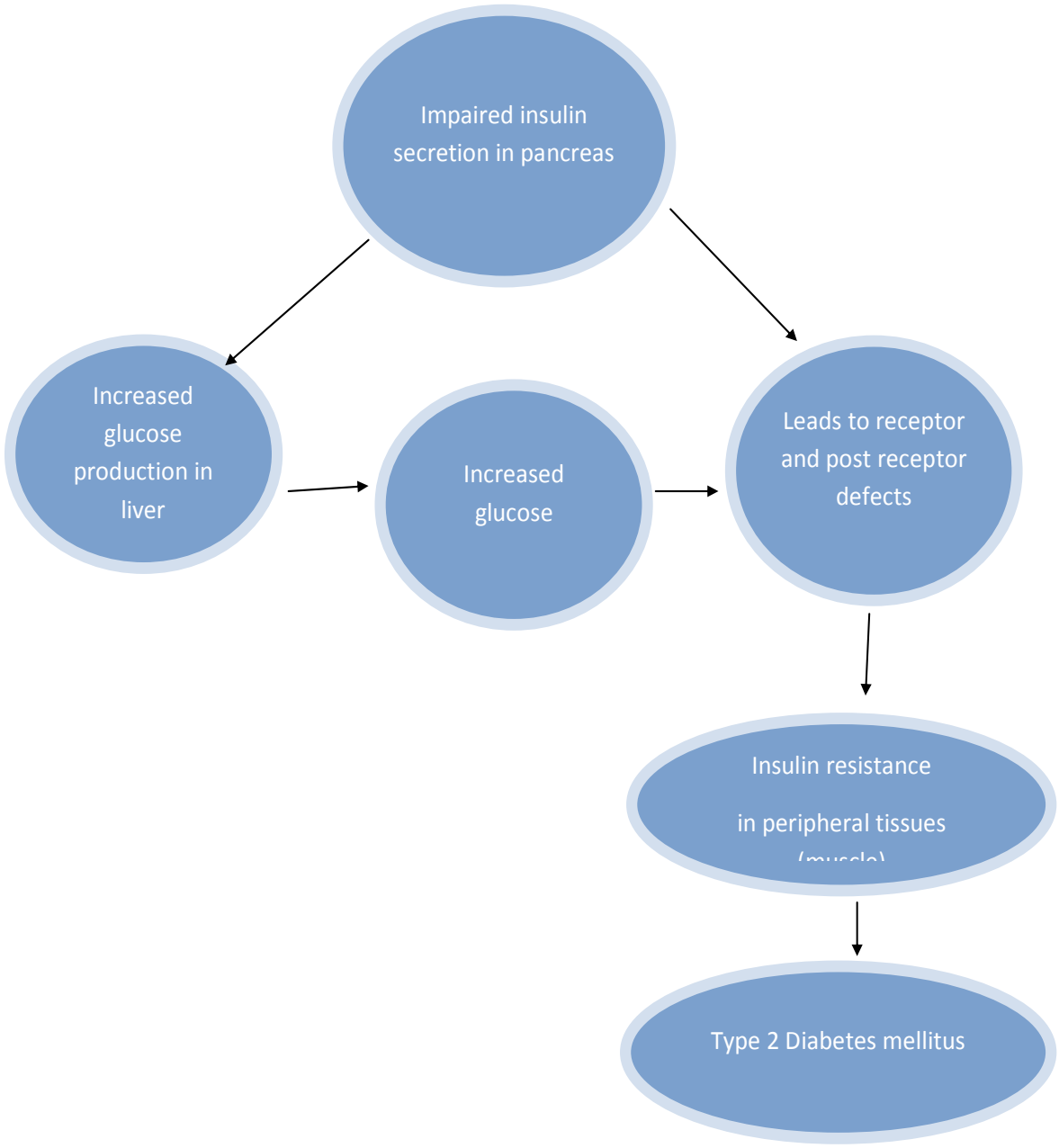

Figure 3. Pathophysiology of type 2 diabetes mellitus.

worldwide, it is necessary to have an improved understanding of its etiology, pathogenesis and pathophysiology to focus therapeutic and research efforts appropriately. A coordinated multidisciplinary approach is needed that involves scientists, public health practitioners, educators, clinicians and diabetics, with support from government authorities and nongovernmental organizations to reduce the incidence of diabetes significantly.

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Full Length Research Paper

Knowledge of computer vision syndrome among computer users in the workplace in Abuja, Nigeria

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Quantitative, descriptive, cross-sectional study was conducted to determine the level of knowledge and extent of computer vision syndrome (CVS) among computer users at the Securities and Exchange Commission (SEC), Abuja, Nigeria. Structured questionnaire was administered to 100 computer users aged between 18 and 40 years. The findings showed that 40% of the participants were aware of CVS; of which 27% had knowledge of the disorder. CVS was common among the employees, 74% of the respondents experienced at least one symptom of CVS. Headache and eyestrain were the most common symptoms of CVS among the studied population. The study concluded that there is a serious knowledge gap about CVS in the studied population which suggests a similar knowledge gap in the general population. It is recommended that further studies on a large scale should be carried out to explore the extent and knowledge about CVS in the developing countries for the purpose of designing strategies for bridging-up the knowledge-gap and minimize the impact of CVS on the people at risk.

Key words: Computer vision syndrome, knowledge, awareness, computer users.

INTRODUCTION

When the first IBM personal computer was manufactured in 1981, the company did not envisage the possible potential health hazards the users may consequently experience (Mvungi et al., 2009). Today, a condition known as computer vision syndrome (CVS) is common to millions of computer users around the world. At present, a large number of computer users suffer from CVS (Ihemedu et al., 2010; Sen and Richardson, 2007; Torrey, 2003). In the USA more than 143 million Americans work on a computer each day with an estimated 90% suffering from computer eyestrain. Additionally, almost 90% of children in the USA work on a computer at home or in school every day (LFV, 2007; Vision Council (VCA), 2007).

CVS remains an underestimated and poorly understood condition at the workplace (Izquierdo et al., 2004; Izquierdo, 2010). About 70% of computer workers worldwide report having vision problems and there is an alarming increase in the number of people affected (Blehm et al., 2005). CVS is caused by the eye and brain reacting differently to characters on the screen than they do to printed characters. The computer screen constantly refreshes at a certain rate whereas paper is steady and the characters on a computer screen lack the contrast or well defined edges that printed characters have. Therefore, the colour intensity of digital characters diminishes around the edges making it difficult for eyes to remain focused. Having to continuously refocusing on digital text fatigues the eyes and can lead to burning or tired eyes (Blehm et al., 2005; Anshel, 2005). The condition is marked by symptoms such as eyestrains, burning sensation, blurred vision, gritty sensation, headache and neck pains. Some computer users may experience continued reduced visual abilities such as blurred distant vision even after work (Chiemeke et al., 2007). The symptoms may be aggravated by

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poor lighting, glare, improper work station set up and uncorrected refractive errors (Ihemedu and Omolase, 2010; Torrey, 2003).

In Africa, not many studies on CVS have been carried out in spite that computer use has attained a significant patronage especially with the upsurge of information and communication technology. Consequently, many organisations can barely manage their businesses without the computer. Poor publicity and utilisation of preventive measures however, have hampered the effectiveness of computers due to the overwhelming symptoms experienced by some users (Ihemedu and Omolase, 2010). Awareness of visual problems from computer use has also been minimally stressed in most industrially developing countries like Nigeria (Chiemeke et al., 2007). Some researchers (Divjak and Bischof, 2009; Mvungi et al., 2009) have explained that CVS can be avoided by suitable preventive actions, but majority of the sufferers are ignorant of this. In the basis of this, some eye care professionals have referred to CVS as the number one occupational epidemic of the 21st century (Graney, 2011; Torrey, 2003).

A study by Chiemeke et al. (2007) in Benin, Nigeria tested the respondents' knowledge on computer ergonomics and preventive measures of CVS. Results from the study showed that only a small percentage (32%) of the respondents was aware of preventive measures for visual symptoms, while a minority (1%) had former ergonomics guidelines/policies at their workplace. Similar studies in South-West Nigeria (Ihemedu et al., 2010) show that a large number of respondents were aware of various types of computer shields but only a few utilised the shields. Studies from other parts of Africa show that most problems associated with computer use are caused by insufficient knowledge about safe computer usage (Mvungi et al., 2009).

Mounting evidence shows that CVS can significantly harm workplace productivity, as it places an unusual strain on the human physical well-being thereby reducing the quality of life (Torrey, 2003). Previous studies (Izquierdo et al., 2004; Chiemeke et al., 2007; Divjak et al., 2009) have demonstrated a direct correlation between proper vision correction and the time required for a computer worker to complete a task; and that productivity is reduced even more among computer users who were unaware that they had vision problems. CVS is therefore a significant public health problem as it affects computer users from all walks of life (Torrey, 2003).

The main purpose of the study was to assess the knowledge of computer users about CVS in a workplace in Abuja, Nigeria. The study specifically explored the level of knowledge and awareness about CVS among computer users and determined the extent of CVS by assessing the visual symptoms among the study population. This study aims to contribute evidence-based information on CVS in Nigeria and the findings would assist employers and other stakeholders to develop strategies that will be used to reduce the effects of CVS in the selected population. Training institutions and health educators will find the results of this study useful in developing and revising training curricula that will enhance knowledge and level of awareness of CVS among computer users in Nigeria.

METHODOLOGY

A quantitative, descriptive cross-sectional study was conducted to assess the level of knowledge about CVS and its preventive measures among the staff members of the Securities and Exchange Commission (SEC), Abuja. The study population included both male and female adults (18 to 40 years) working at the SEC office. Simple random sampling was used to select the study sample from the sampling frame by assigning numbers to the sampling frame then numbers were randomly selected to obtain the study sample. Data was collected with the help of two research assistants using a semi-structured questionnaire containing 22 items developed by the researcher using question items from previous studies (Onunkwor, 2011). The research instrument was pre-tested on respondents from the Central Bank of Nigeria, Central Area, Abuja who were comparable to the sample of correspondents, but were not part of the main study. Data was analysed using Epi-info version 7 (2011) software. Descriptive statistics was used to organise, describe and synthesize the data generated in order to facilitate understanding about knowledge on CVS and inferential statistics was used to test the relationship between knowledge of CVS and demographic factors such as age, gender and level of education. Univariate chi-square tests were used for data analysis. A two-tailed 'p' value of less than 0.05 was considered statistically significant. Permission to carry out the study at the site was given by the SEC in Abuja and the study received ethical clearance DIS 4986 from the University of South Africa (UNISA) Health Studies Higher Degrees Committee.

RESULTS

Data was collected from 100 (54 male and 46 female respondents) employees of the SEC, Abuja over a three-week period from December 2011 to January 2012. The age distribution of the respondents is presented in Table 1. Most employees (84%) were between the ages of 25 and 39 with a mean age of 31 years.

Figure 1 presents the average number of hours respondents spend on the computer daily. Most respondents (45%) spend 6 to 8 h on the computer daily, followed by those who spend 3 to 5 h (33%), more than 8 h (17%) and 1 to 2 h (4%). No respondent indicated less than 1 h.

The duration of computer use is as shown in Figure 2. Only 6% of the respondents had used the computer for less than 1 year; 15% had been using the computer for between 1 and 2 years; 28% have used the computer for duration of 3 to 5 years. About 29 and 20% have been using the computer for between 6 and 8 years, and more than 8 years, respectively.

In this study the term 'awareness' was used to mean having heard of CVS. Respondents' were asked the question 'are you aware of a condition called computer vision syndrome?' One respondent did not answer this

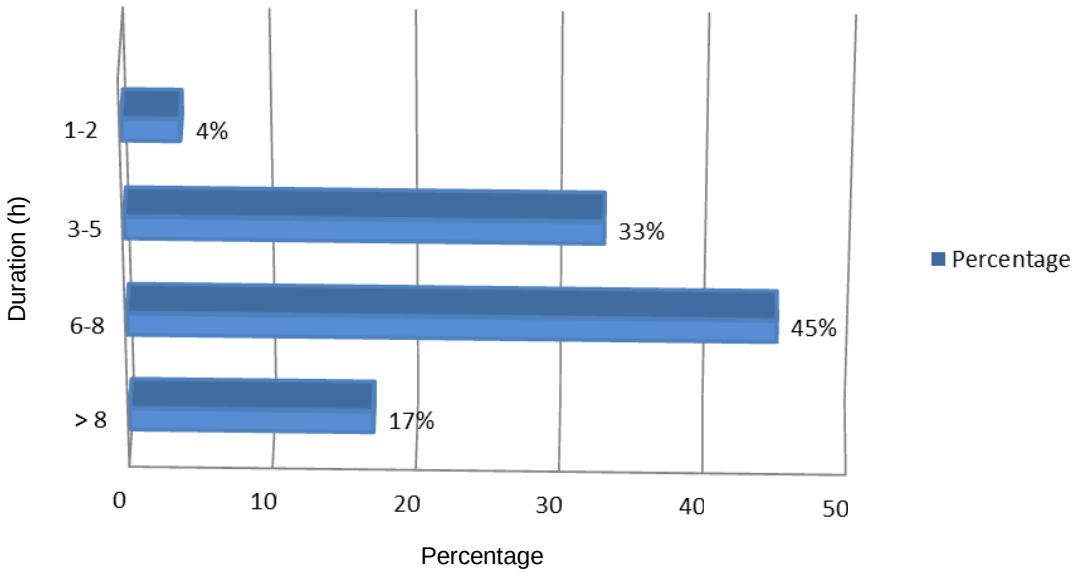

Figure 1. Bar chart showing the average hours spent by SEC, Abuja, Nigeria employees on computer daily.

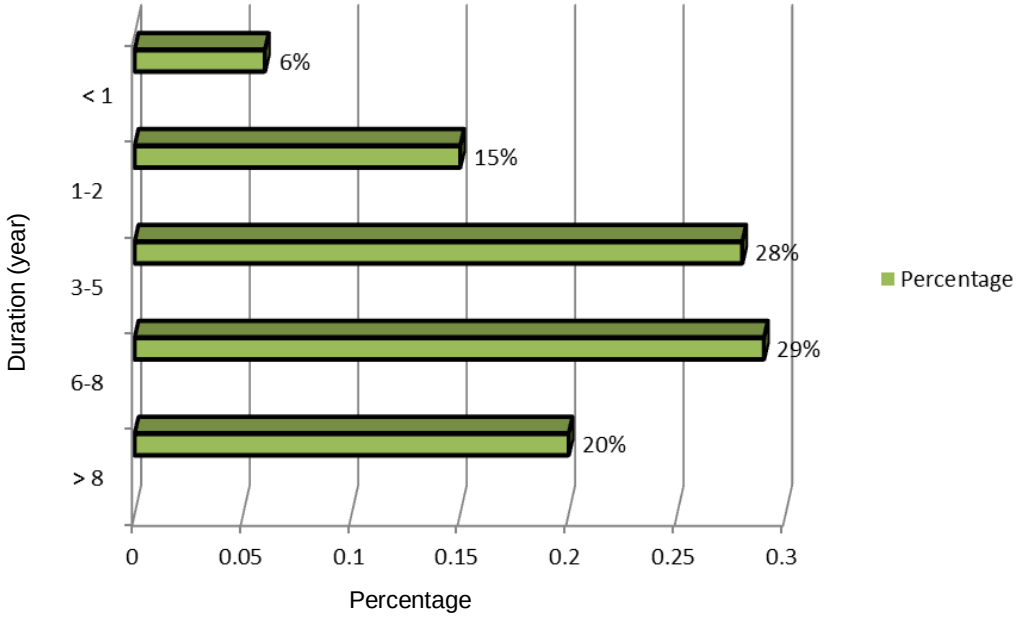

Figure 2. Bar chart showing the duration of computer use by SEC employees, Abuja, Nigeria.

question, 40 admitted to be aware of the syndrome and about 60% had not heard of CVS.

Knowledge of CVS in this study is defined as acknowledging having some understanding of CVS by selecting the options presented in Table 2. Out of the 40 respondents that indicated 'yes' to the awareness of CVS, 2 respondents (5%) indicated option (i), 1 respondent (2.5%) indicated option (ii), 27 respondents (67.5%) indicated the correct option (iii), and 10 respondents (25%) indicated option (iv). The knowledge about CVS was increasing with age, with the age group 35 to 39 years having the highest knowledge about CVS.

The frequencies of CVS symptoms experienced by the respondents are as shown in Figure 3. About 74% of the study population indicated 'Yes' to at least one symptom experienced during computer use; 25% indicated 'No' to all the symptoms and 1% did not indicate either 'Yes' or 'No'. The symptoms most experienced are headache

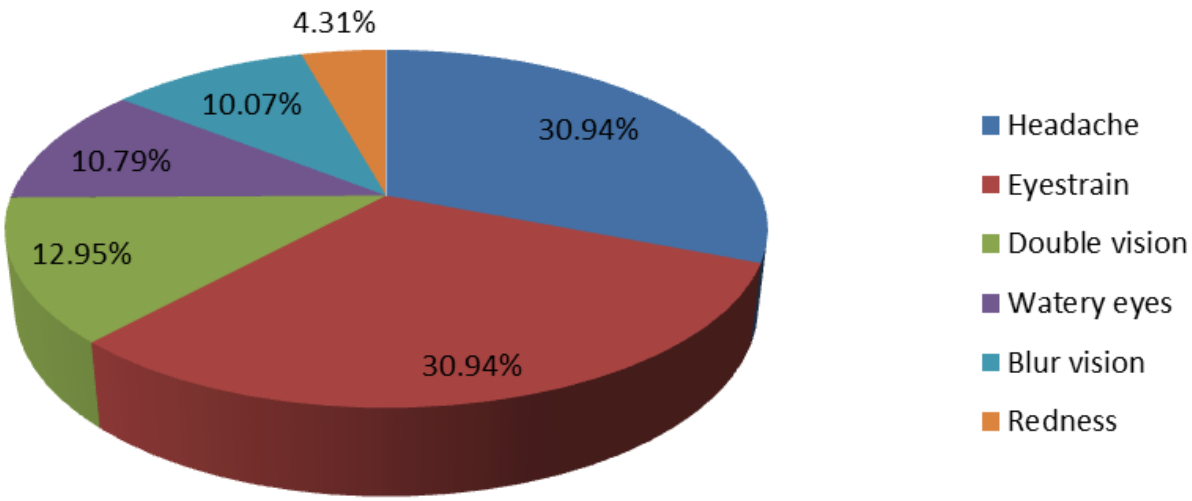

Figure 3. Pie chart showing the frequency of CVS symptoms among SEC employees in Abuja, Nigeria.

Table 1. The age distribution of the respondents from SEC, Abuja, Nigeria.

Age group (Years)	Frequency	%	Cumulative (%)
18-20	1	1	1
21-24	15	15	16
25-29	26	26	42
30-34	25	25	67
35-39	33	33	100
Total	100	100	-

Table 2. Level of knowledge about CVS among SEC employees, Abuja, Nigeria.

Options	Frequency	Percent (out of 40)	Overall (%)
(i) Tiredness during computer use	2	5	2
(ii) Wearing glasses while using the computer	1	2.5	1
(iii) Combination of headache, eyestrain and blur vision that occur as a result of prolonged computer use	27	67.5	27
(iv) I only heard of it, I don't know what it means	10	25	10

(30.94%) and eyestrain (30.94%). Double vision was experienced by 12.95%, watery eyes were reported by 10.79%, blur vision and redness were experienced by 10.07 and 4.31%, respectively.

The relationship between the average number of hours spent on the computer and CVS symptoms among the study population is presented in Table 3. CVS symptoms were reported more commonly among the employees who spent 6 to 8 h on the computer daily (48.9%) as compared to 23.7 and 0.72% among those who spend 3 to 5 h and 1 to 2 h, respectively. A similar trend is seen on the relationship between CVS symptoms and the duration of computer use.

Prevention of CVS is a priority in minimizing the impact of CVS on employee's productivity. Table 4 summarizes the responses of the employees on the preventive measures. Taking regular breaks, regular eye checks and using computer glare screen were the commonest preventive measures which together accounted for 94.4%.

DISCUSSION

The 21st Century is characterised by rapid developments in information technology. With dependency on information technology, the computer has become a common tool in schools, colleges, universities and workplaces. According to the American Optometry Association, CVS is defined as "the complex of eye and vision problems

Table 3. The relationship between CVS symptoms and the average number of hours spent on computer by SEC employees, Abuja, Nigeria.

Duration (h)	No. of respondents	Headache	Eyestrain	Double vision	Redness	Watery eyes	Blur vision
1-2	4	-	1	-	-	-	-
3-5	33	8	15	3	2	2	3
6-8	45	24	16	12	3	7	6
>8	17	11	11	3	1	5	5
No answer	1	-	-	-	-	1	-

Table 4. The preventive measures of CVS as selected by the SEC employees, Abuja, Nigeria.

Option	Frequency	Percent
(a) Taking regular breaks	40	32
(b) Blinking frequently	7	5.6
(c) Checking eyes regularly	39	31.2
(d) Using glare screen on the computer	39	31.2

related to near work which are experienced during or related computer use" (AOA, 1995). Currently CVS affects millions of people globally (Sen et al., 2007; Rathore et al., 2011; Chakrabarti, 2007) and is increasingly becoming a public health concern. Different terms have been used to describe symptoms of CVS, such as visual discomfort, ocular disorder and visual difficulty. In general, the CVS symptoms can be divided into three categories (1) eye-related symptoms e.g. dry eyes, watery eyes, irritated eyes, (2) vision-related symptoms e.g. eye strain, eye fatigue, headache, blurred vision, and (3) posture-related symptoms e.g. sore neck, shoulder pain, sore back (Blehm et al., 2005; Sheddy, 2000). Since CVS manifests with a variety of symptoms, researchers in optometry and ergonomics have developed diagnostic procedures and treatment including a comprehensive eye/vision examination of computer users at the beginning and on regular basis, on-site ergonomic evaluation and instruction on correct working habits, use of proper computer glasses, frequent breaks, training computer users to blinking frequently when using computers and administration of artificial tears usually resolve the problem of mild to moderate dry eyes (Acosta et al., 1999; Tsubota, 2002; Biswas et al., 2003).

Unfortunately, CVS has not been studied extensively in Nigeria and other developing countries. This study was carried out to explore the level of knowledge about CVS among employees of the SEC in Abuja, Nigeria.

It has been shown in this study that most employees use computers on daily basis and the duration of use ranged between 1 and more than 8 h per day. It has also been observed that CVS is common among the studied population with about 74% of the participants experience-ing at least one of the CVS symptoms. The most experienced symptoms were headache and eye strain which together accounted for 61.8%. Other symptoms reported were double vision, watery eyes, blur vision and eye redness. Our findings are in agreement with the report by Bali et al. (2007) who reported eyestrain (97.8%) and headache (82.1%) as chief presenting symptoms of CVS in their study population. Similarly, the findings in this study concur with the findings by Chiemeke et al. (2007) who reported eyestrain as being the most common visual symptom experienced by computer users. They also reported blurred distance vision, headache, double vision and redness of eyes as other common visual symptoms associated with computer use.

It has been observed in this study that respondents that spend 6 to 8 h average daily on the computer experience more CVS symptoms (48.9%), followed by respondents that spend more than 8 h daily (25.9%) and 23.7% by respondents that spend 3 to 5 h daily on the computer. Respondents that spend 1 to 2 h daily experience the least symptoms of CVS (0.72%). This finding is similar to previous findings (Ihemedu et al., 2010) who reported that more symptoms were noticed amongst the computer users in the university and hospital as compared to the bankers who tend to spend longer time on computers. Our study has further shown that the longer the duration in years of computer use, the more the CVS symptoms, because respondents that have been using computer for less than 1 year experienced the least symptoms (1.4%) when compared with those who have been using computer for between 6 and more than 8 years (31.7%). The findings support that the symptoms are related to computer use and can be experienced from use of computer at short period of between 1 and 2 h. The reduced number of symptoms among employees using the computer for more than 8 h can be explained by

possibly some forms of compensatory mechanisms to chronic exposure that occurred resulting in loss of sensitivity and the employee responds less.

Sufficient knowledge about CVS and its preventive measures would help reduce the incidence in a population. Extensive literature search did not reveal any publication on knowledge of CVS, thus making comparison with other results difficult. Chiemeke et al. (2007) reported that 32% of the respondents in their study were aware of preventive measures for computer-related visual symptoms. While majority of the participants in this study were literate, the level of knowledge about CVS was very low (27%) suggesting a serious knowledge gap exists about CVS in the studied population and possibly in the general population. The respondents indicated the possible causes of the symptoms include tiredness during computer use and an indication to wear spectacles. Taking regular breaks, regular eye sight checks and using glare screen on computer were selected by the participants in the study as the most commonly used preventive measures. However, and interestingly, frequent blinking is much more easily applicable was least considered to be preventive.

CVS has been classified as the number one occupational hazard of the 21st Century (Torrey, 2003). This observation cannot be overemphasized when considering the upsurge in information technology, proliferation of computer systems, dependency on the computer for daily operations and occurrence of CVS among employees. It is so now, because in 2000 it was reported that more than 75% of daily activities of all jobs involve the use of the computer (Ihemedu et al., 2010).

CVS significantly impairs workplace productivity and reduces the quality of life by placing unusual strain on the human physical well-being. Unfortunately, both the level of awareness and knowledge of CVS among the studied population were unsatisfactory at 40 and 27%, respectively. It is recommended that further studies be carried out on a large scale to determine the extent of the CVS problem among employees at workplaces including schools, colleges, higher education institutions, government departments and the private sector in Nigeria. It is envisaged that such evidence-based information will be used by stakeholders to raise awareness about CVS among the workforce and for designing intervention strategies to reduce the impact of CVS at workplaces.

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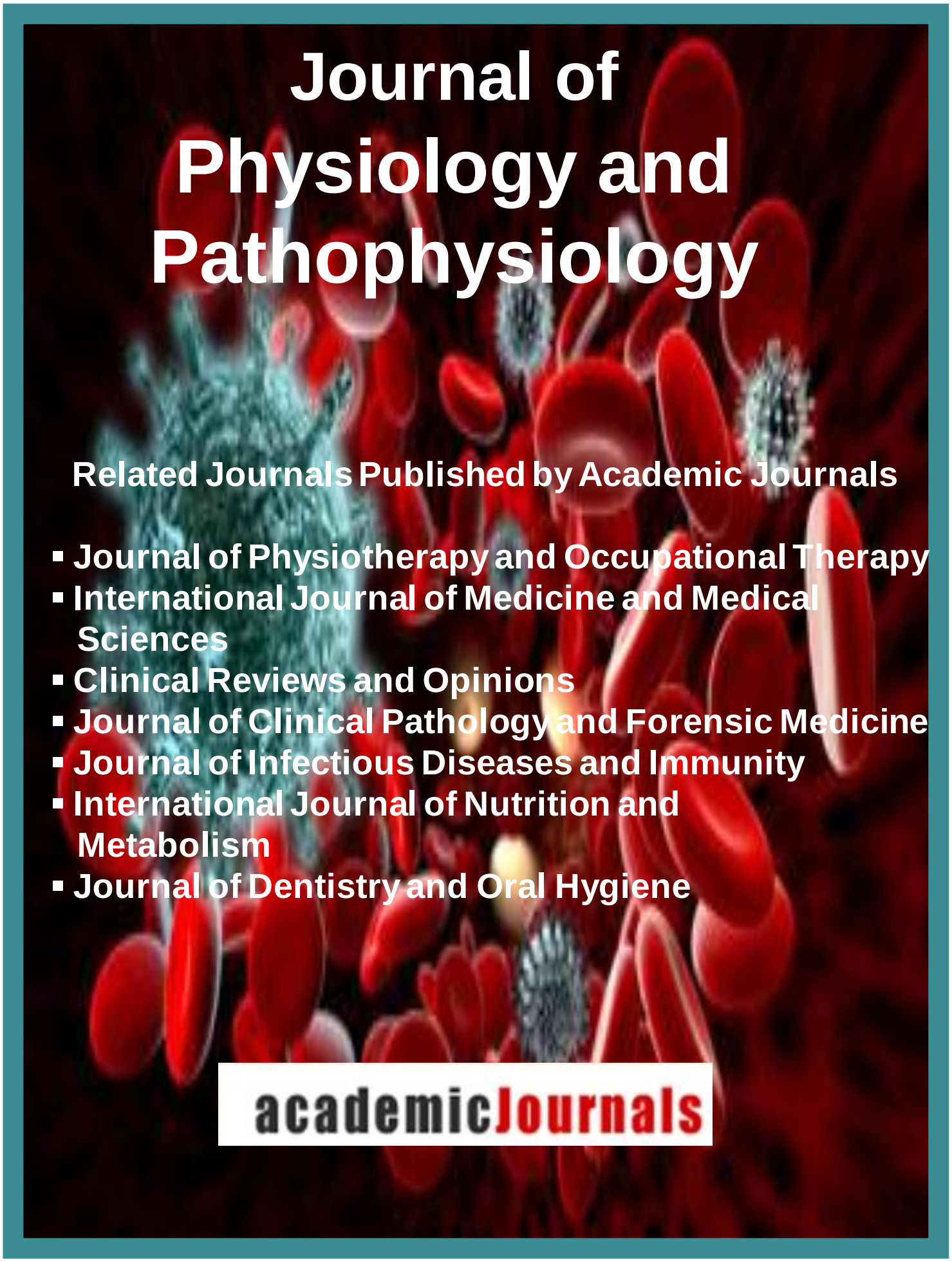

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