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DIABETES MELLITUS, OBESITY AND ADIPOCYTOKINES: PATHOPHYSIOLOGICAL PERSPECTIVES

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ABSTRACT

Diabetes mellitus is classified as type-1 diabetes mellitus (T1DM), type-2 (T2DM), gestational diabetes, and other specific types of diabetes mellitus. It is a group of complications or disorders leading to a variety of physiological, metabolic, physiochemical and behavioral alterations. Weight loss targets/ programs can be established with the important role of nurse practitioners in clinical practice since they have in-depth awareness of the research in diverse aspects of obesity/ weight management. Furthermore, overweight and obese conditions are alarming risk factors for most of the T2DM patients that requires the implementation of better primary care and all possible strategies. There are a variety of risk factors, causes and diverse issues in diabetes mellitus. The present review study was conducted to have better awareness in the cellular and molecular Pathophysiology of diabetes mellitus by studying the impact and interaction of leptin and adiponectin in patients having diabetic mellitus with/ without obesity. However, in view of controversial reports, further more detailed studies are required to understand the impact and role of adipocytokines and obesity in patients with diabetes mellitus. Conclusively, the present review provides opportunity for understanding the better knowledge of diabetic disorders.

Key words: Diabetes mellitus, obesity, adipocytokines, leptin, adiponectin, Pathophysiology

INTRODUCTION

Diabetes mellitus is classified as type-1 (T1DM), type-2 (T2DM), gestational diabetes, and other specific types of diabetes mellitus. It is a group of complications or disorders leading to a variety of physiological, metabolic, physiochemical and behavioral alterations. There are nice recent reviews and studies describing the various facets of diabetes mellitus (Unnikrishnan *et al*., 2016; Fatima *et al*., 2017a; Kodama *et al*., 2017; Tiwari *et al*., 2018; Steinberg and Carlson, 2019).

Diabetes mellitus involves either disorder in the insulin secretion, action or rather both. It appears in three forms: type 1 diabetes mellitus (T1-DM), type 2 diabetes mellitus (T2-DM) and type 3 or gestational diabetes mellitus. The most common type of diabetes, however, is T2-DM wherein obesity, physical inactivity, family history, age and certain ethnicities are prevalent risk factors. The nomenclature and conceptual definitions of diabetes were established in the form of a document (National Diabetes Data Group, 1979) and confirmed by the authorities (WHO Tech. Report 1980, 1985) and named initially as NIDDM and IDDM respectively for "noninsulin-dependent diabetes mellitus" and "insulin-dependent diabetes mellitus". In view of the confusions appearing after the discovery of other sub-types of diabetes, later classification comprised new names: type1, 2 and 3 diabetes mellitus. Hyperglycemia, however, remained the main manifestation in all types of diabetes mellitus beside other diagnostic criteria.

There are a variety of risk factors, causes and diverse issues in various disorders occurring in diabetes mellitus. However, the present review has been prepared to have further awareness in the pathophysiology of diabetes mellitus by studying the impact and interaction of two important adipose tissue secretions- leptin and adiponectin; and lipid profile and physiological aspects in diabetic patients with/ without obesity. We already have published some of our research work (Hussain *et al*., 2007a; Sohail *et al*., 2013) and review articles (Hussain *et al*., 2007b; Sohail and Hussain, 2013) in that perspective. Some of the related work of our collaborators (Ashraf *et al*., 2006; Basir and Ashraf, 2007; Ashraf and Basir, 2007) was also quite interesting.

The literature presents excellent articles in connection with the role of leptin, adiponectin, lipid profile and related physiological aspects in diabetes mellitus with/ without the risk facors of obesity (Caro *et al.*, 1996; Maeda *et al*., 1996; Kawakami *et al*., 1997; Shimomura *et al*.,1999; Roden *et al*., 2000; Habib and Aslam 2003; Veniant and LeBe, 2003; Martin *et al*., 2008; Chrzanowska *et al.*, 2011; Nayak *et al*., 2012; Oh *et al*., 2012; Gardener *et al*., 2013; Ostrowska *et al*., 2013; Al-Hamodi *et al*., 2014; Benbaibeche *et al*., 2014; Benedict *et al*., 2014; Fatima *et al*.,

2014; Gray *et al*., 2014; He *et al*., 2014; Lacobellis *et al*.,2014; Farr *et al*.,2015; Hossain *et al*., 2015; Kurajoh *et al*., 2015; Prakash *et al*., 2015; Unnikrishnan *et al*., 2016; Kodama *et al*., 2017; Tiwari *et al*., 2018; Steinberg and Carlson, 2019).

It is not easy to study the patients with diabetes mellitus having various risk factors. Hence, mostly researchers study the diabetes patients with/ without obesity as a risk factor. The literature showed the studies and specific aspects already carried out emphasizing the involvement of adipokines and obesity in diabetes mellitus (Verrotti *et al*., 2000; Nakano *et al*., 2012; Oh *et al*., 2012; Patel *et al*., 2013; Wang *et al*., 2013b; Benbaibeche *et al*., 2014; Gu *et al*., 2014; Gardener *et al*., 2013; Maekawa *et al*., 2013; Morioka *et al*., 2014; Najam *et al*., 2014; Chearskul *et al*., 2015; Musil *et al*., 2015; Pandey *et al*., 2015; Mohammad and Ahmad, 2016; Bouter *et al*., 2017; Cui *et al*., 2017; Qadir and Ahmed, 2017; Xu and Tong, 2017; Fruh, 2017; Abdella and Mojiminiyi, 2018; Afarid *et al*., 2018; Katsiki *et al*., 2018; Volaco *et al*., 2018 ; Bulum *et al*., 2019; Farkhondeh *et al*., 2019; Liaset *et al*., 2019; Rydén *et al*., 2019; Zhang *et al*., 2019), impact of lipid profile in diabetes mellitus (Connelly *et al*., 1999; Seller*set al*., 2007; Preis *et al*., 2009; Aryal *et al*., 2010; Ram *et al*., 2014), and role of lipid profile in diabetic patients with obesity (Kumar *et al*., 2013; Owecki *et al*., 2007; Wang *et al*., 2013a; He *et al*., 2014).

The mentioned studies help carrying out further work by determining, analyzing and correlating the factors which may be interacting each other and those involved some way in the pathophysiological processes leading to disordered conditions in diabetes mellitus with / without obesity. This explores multidisciplinary approach of investigating the causes and effects, and their precise interactions that might provide more knowledge of multifactorial diseases.

In view of controversial reports in literature, we studied the role of leptin and adiponectin, lipid profile and other important physiological factors in diabetes mellitus with/ without obesity (Sohail, 2015), employing relevant statistical methods (Zahir *et al*., 2014). However, further comprehensive and more well controlled studies are required for investigating the precise involvement of adipokines in diabetes mellitus with/ without obesity. Although there are a variety of factors at clinical, physiological, cellular and molecular level that are considered important in diabetology, present review presents selected literature with better controls for elucidating the precise role of these factor in diabetes mellitus.

This review study is hence, important in applying the basic studies for understanding the clinical, diagnostic, therapeutic and pathophysiological aspects. Conclusively, the present review study may provide us opportunity to understand the better knowledge of diabetic disorders.

DIABETES MELLITUS

A variety of information is available in diabetes mellitus. Most of the diabetics in Pakistan have no awareness of diabetes and its complication mainly the poor glycemic control and atherogenic dyslipidemia that are high prevalent in T2DM in Pakistan (Habib and Aslam, 2003). Hypothyroidism was found associated with gestational diabetes (Fatima *et al*., 2016a). It has recently been suggested that employing STEPS (safety; tolerability; efficacy; price; simplicity) criteria, metformin is the first line option additionally with other medication for diabetes mellitus type-2 (T2DM) patients (Steinberg and Carlson, 2019). It was suggested that unstable body-weight might be associated modestly with increased risk of T2DM (Kodama *et al*., 2017). Increased prevalence in youth with even low BMI, and complications of T2DM in India have been characterized as different from those in white people (Unnikrishnan *et al*., 2016). We carried out research studies in several aspects of diabetes mellitus (Hussain, 1998; Sohail and Hussain, 2008, 2009; Sohail *et al*., 2017).

It was found that body weight both in diabetic and non diabetic subjects using low carbohydrate diet was reduced more effectively than in those using healthy diet, and the weight loss in those using low carbohydrate diet was greater, while no variation in HbA(1c), lipids and ketone (Dyson *et al*., 2007). Plasma leptin correlated with cholesterol levels and LDL in T2DM (Roden *et al*., 2000). Two sub-types in hyperglycemic black non-insulin-dependent diabetic (NIDDM) population were i) those having insulin resistance and ii) those having normal insulin sensitivity and representing 40% with BMI less than 30 kg / m^2 and having lower cardiovascular risk (Chaiken *et al*., 1991).

Comparisons among all ethnics in the Caribbean T2DM groups were carried out (Nayak *et al*., 2012) that provides the role a variety of factors in T2DM. The levels of adiponectin and fat mass were significantly different between male and female subjects (Prakash *et al*., 2015). High density lipoprotein cholesterol (HDL-C) was lower in Trinidadian type 2 diabetic subjects (Nayak *et al*., 2012). Role of adiponectin (Prakash *et al*., 2015) and lipid profile (Nayak *et al*., 2012) in T2DM was studied quite precisely.

Genetic aspects in gestational diabetes in Pakistani women in relation to higher glucose level and insulin resistance have been studies (Fatima *et al*., 2016b). ADIPOQ (genes encoding adiponectin) and its receptors are not found to be involved in causing the risk of insulin resistance but associated with diabetes type 2 in European-

Australians (Peters *et al*., 2013). Some of the important factors associated in Trinidadian type 2 diabetics considering age, gender, and ethnicity were HDL-cholesterol and low adiponectin levels (Nayak *et al*., 2012). Family history of diabetes could be a risk factor in diabetes type 2 in obese Korean children especially with low levels of serum adiponectin (Oh *et al*., 2012). Significance of microRNAs or miRNAs in view of susceptibility towards β cells transcriptional activity in pancreas has been indicated to understand the complicated molecular pathophysiological mechanism in T2DM (Tiwari *et al*., 2018).

Lipid profile components especially TC, LDL-C and HDL-C and HDL-C subfractions associated significantly with age and HbA1c in both sexes with T1DM (Idzior-Walus *et al*., 2001). Plasma leptin correlated with age in T1DM (Roden *et al*., 2000). Measuring central obesity, it was found that men subjects with T1DM showed age and HbA1c adjusted values of TG, TC, LDL-C, HDL-C and HDL3-C significantly associated with central obesity (Idzior-Walus *et al*., 2001). The degree of physical activity in men with T1DM was positively with HDL-C and HDL3-C (Idzior-Walus *et al*., 2001). Furthermore, measuring central obesity, it was found that women subjects with T1DM showed HDL-C significantly associated with central obesity (Idzior-Walus *et al*., 2001). Plasma leptin correlated with triglycerides levels in T1DM (Roden *et al*., 2000). Smoking and central obesity influenced the lipid profile in T1DM (Idzior-Walus *et al*., 2001).

It was noted that only female T1DM and T2DM also had influenced leptin in relation to BMI compared to non-diabetic females (Roden *et al*., 2000). Comparisons in all groups of diabetics showed that age-adjusted correlation of plasma leptin with body mass index and sex but not with glycosylated haemoglobin A1c were obtained (Roden *et al*., 2000).

OBESITY

To explain the mechanism of the occurrence of obesity, association of visceral fat accumulation with autonomic dysfunction has been mentioned (Kurajoh *et al*., 2015). The mechanisms whereby the common polymorphisms in fat mass and obesity-associated gene (FTO) carry out the development of human obesity are not clearly known (Benedict *et al*., 2014). Obesity results from genetic/ epigenetic/ metagenomic and environmental reasons or disordered interplay among these factors (Pigeyre *et al*., 2016). It has been shown that combination therapy of tofogliflozin and pioglitazone was found to decrease the pioglitazone-induced body weight gain and decrease the glycated hemoglobin more effectively than single therapy with pioglitazone or tofogliflozin alone (Suzuki *et al*., 2014). Our own work in obesity provide significant investigations (Hussain, 1991d, 1992c, 2010; Hasan *et al*., 2011; Serafi *et al*., 2018; Rehman *et al*., 2012, 2013a, 2013b; 2015, 2016; Sohail, 2015).

Appearance of dysfunction and complications of obesity relates to quantity and type of food nutrients consumed and their effect on tissues and organs for manifesting overall health (Duwaerts and Maher, 2019). High fat low carbohydrate (HFLC) diet in obese subjects had greater improvements in blood lipids, body weight and systemic inflammation compared to low fat high carbohydrate (LFHC) diet in obese subjects (Ruth *et al*., 2013). The High fat low carbohydrate (HFLC) group showed greater mean increases in HDL cholesterol relative to the LFHC in obese subject groups (Ruth *et al*., 2013).

In the perspective to familial involvement, the subjects with AA genotype of rs2805533 comprised greater abdominal circumference, higher level of body mass index, and lower adiponectin level relative to those in AG and GG genotypes. This shows that abdominal obesity and lipid profiles are the intermediary major factors whereby genetic factors regulate obesity (Oguro *et al*., 2012). The High fat low carbohydrate (HFLC) group showed lipid profile alterations in obese subject groups (Ruth *et al*., 2013).

Proper management of the childhood obesity requires healthy life style of the individual and family and long-term care with high-intensity behavioral interventions (Anderson, 2018). Understanding association between obesity and weight-loss and life-style/ health quality is essentially required for the proper management of obesity (Kolotkin and Andersen, 2017). Management of obesity requires behavioral therapy, pharmacotherapy, bariatric surgery and other approaches, though the treatment may lead to weight loss that needs to be especially managed (Heymsfield and Wadden, 2017).

LEPTIN

Leptin is an adipocyte derived cytokine and hormone that is quite important for the cardiovascular health (Martin *et al*., 2008). The action of leptin in controlling the energy metabolism is quite established (Kalra 2009). Leptin derived from adipocyte controls glucose metabolism and other energy homeostasis (Nakano *et al*., 2012). Some of the peripheral effects of leptin are mediated through CNS and others through direct action on peripheral tissue targets (Veniant and LeBe, 2003). Some of our own studies provide interesting investigations about leptin, adiponectin and other adipocytokines (Hussain *et al*., 2007b; Serafi *et al*., 2013, 2016, 2018; Sohail and Hussain, 2013; Sohail, 2015).

Changes in leptin levels immediately after birth upto 24 h postnatally in lambs showed association with the body temperature, environmental temperature, plasma lipids, blood glucose, and 3-beta-hydroxybutyric acid (Schilling 2015). Leptin has a variety of functions including regulating metabolic homeostasis, increasing glucose uptake, decreasing the production of glucagon and corticosterone, inhibiting food intake, increasing energy expenditure, inhibiting hepatic glucose output all that shows the role of leptin in diabetes, but how leptin regulates the blood glucose is still not fully understood (D'souza *et al*., 2017).

Regular provision of required leptin level during development assists in the occurrence of normal maturation, metabolism, and growth of tissues, and hypo or hyperleptinemia cause developmental programming complications requiring therapeutic involvement and leptin in postnatal and later life period (Vikers, 2007).

Genetic mutation, cellular and circulating leptin regulation, less access of leptin, and self regulation by leptin are some of the mechanisms of leptin resistance (Martin *et al*., 2008). Insulin is counterregulated partly by leptin as an important factor of autonomic control of body weight via inhibiting insulin secretion, decreasing insulin lipogenesis by leptin lipolysis, potentiating cholecystokinin mediated satiation by leptin, and controlling the brain and peripheral tissue sensitivity to insulin action (Borer, 2014). Leptin can interact with insulin, interleukin-6 and other innate immunity mediators (Martin *et al*., 2008). Leptin, expression and the regulatory mechanisms of leptin via insulin and other hormones have been found quite important in health and disease (Schanton *et al*., 2018).

Beside the involvement of leptin in obesity and diabetes, it effects also the processes including thermogenesis, appetite, reproduction and immune system, and it acts directly on specific tissues including neuron, muscle and liver and metabolism (Veniant and LeBe, 2003). Leptin has an important role in inflammation, inflammatory conditions and autoimmune diseases (La Cava, 2017).

ADIPONECTIN

Association of adiponectin with atherosclerosis and cardiovascular disease has recently been discussed (Hossain *et al*., 2015). The levels of adiponectin were significantly different between male and female subjects (Prakash *et al*., 2015). Women had higher concentration of adiponectin than men (Ostrowska *et al*., 2013). Lower levels of adiponectin levels were found in male subjects than female subjects (Gardener *et al*., 2013). Lower levels of adiponectin levels were found in young subjects and greater levels in old age (Gardener *et al*., 2013). Adiponectin levels were found greatest among whites, then followed by Hispanics, and lowest in blacks (Gardener *et al*., 2013). Lower levels of adiponectin levels were found in subjects with elevated waist circumference (Gardener *et al*., 2013).

Some of the factors causing hypoadiponectinemia are mutations in adiponectin genes, single nucleotide polymorphisms (SNPs), obesity or visceral fat deposition (Hossain *et al*., 2015). It was found that variations in genes encoding adiponectin (ADIPOQ), but not its receptors (ADIPOR1/R2) were associated with the altered level of serum adiponectin in European-Australians (Peters *et al*., 2013). Comprehensive review discussion for the management of hypoadiponectinemia indicates the need of adiponectin up-regulation and newer ways for developing potential drugs for clinical management (Hossain *et al*., 2015).

Adiponectin is accepted as the biomarker in obesity related disorders including mainly T2DM, ASCVD (and atherosclerotic cardiovascular disease), and metabolic syndrome (Ramakrishnan and Jialal, 2018). Functional regulation and significant role of adiponectin as a potential therapeutic target/ replacement therapy have been found for the management of obesity, insulin resistance, T2DM, atherosclerosis and other cardiovascular diseases (Achari and Jain, 2017).

DIABETES MELLITUS AND OBESITY

Obesity can increase the insulin resistance leading to heart disease and diabetes (Wang *et al*., 2013b). Tofogliflozin is a highly selective sodium/glucose cotransporter 2 inhibitor that reduces the body weight in obese and diabetics type 2 subjects (Suzuki *et al*., 2014). Comparison of diabetics with non-diabetics per decade showed that diabetics had quite increased BMI (Preis *et al*., 2009).

It has been suggested that tofogliflozin may have the potential effect to prevent obesity, and improve insulin resistance and hyperglycemia (Suzuki *et al*., 2014). It has been revealed that adipocyte impairment due to decreased insulin action and possibility of increased long term risk of T2DM is found in both overweight and obese people (Rydén *et al*., 2019).

The frequency of impaired glucose tolerance was found four times higher in obese subjects with family history of diabetes (FHD) than in obese subjects without family history of diabetes (FHD) (Oh *et al*., 2012). Relationship was determined between obesity indices and lipoprotein levels in the relatives of NIDDM patients (Osei *et al*., 1991). Dyslipidemia in diabetic and non-diabetic patients is associated in separate and combined form with obesity and physical activity (Zhang *et al*., 2019).

Sedentary life-style, hypercaloric diet, genetics and stress-increasing cortisol, growth hormone, glucagon and catecholamine have a link between diabetes and obesity (Volaco *et al*., 2018).It has been emphasized to assess properly the intestinal microbe composition and its role in causing metabolic dysfunction especially obesity and T2DM (Bouter *et al*., 2017). It is essentially required to give due attention on risk factors, complications and ways to manage sustainable long term increased weight/ obesity in a variety of diseases especially diabetes, cardiovascular disorders and cancer (Fruh, 2017).

Management of weight / obesity in patients with T2DM can be established by primary care, however, other strategies involving evidence-based life-style/behavioral/ pharmacological assessments alongwith surgical possibilities are required for the proper management of the diabetic patients having over-weight issue and obesity (Mohammad and Ahmad, 2016).

ADIPOKINES AND OBESITY

Dysregulation in the adipose hormones in obesity has been related to cardiovascular disease, diabetes and other metabolic disorders (Gray *et al*., 2014). A study was conducted to understand the relationship between the circulating adipokines and body composition (Ozias *et al*., 2014) that showed that overweight/ obese women subjects had greater total body fat and abdominal subcutaneous fat than normal-weight women subjects whereas no difference in abdominal visceral fat was obtained. Serum adiponectin decreased in overweight and obese subjects (Benbaibeche *et al*., 2014). Leptin and adiponectin association in type 2 diabetes mellitus for obese versus non-obese correlated directly with BMI (Chearskul *et al*., 2015).

Liver function parameters, cholesterol, and other biochemical changes are associated with adipokine levels in overweight and obese adults that indicate that this information may be used for the establishment of therapeutic targets for the proper prevention and required management of obesity and related disorders (Gray *et al*., 2014).

While studying the replication of obesity and diabetes related single nucleotide polymorphisms (SNPs) in Yucatán, México subjects, it was noted that the association of SNPs rs10485170 of CNR1 and rs5215 of KCNJ11 respectively with adiponectin and leptin, were near significance, whereas a significant association ($p = 0.001$) was found between rs5219 of KCNJ11 and plasma leptin (Hernandez-Escalante *et al*., 2014).

LEPTIN AND OBESITY

Main functions of leptin are to control appetite, energy homeostasis, endocrine regulation/ metabolic hormones, neuroendocrine activities, immune system and obesity (Dornbush and Aeddula, 2018). Leptin is encoded by obese (ob) gene and its circulating levels are found higher in women (Dornbush and Aeddula, 2018). Leptin was found higher in obese subjects (Al-Hamodi *et al*., 2014) and leptin is involved in causing obesity (Veniant and LeBe,, 2003). Leptin in obese subjects was positively correlated with anthropometric measures (Gray *et al*., 2014). Serum leptin increased in overweight and obese subjects (Benbaibeche *et al*., 2014). Higher concentrations of leptin were obtained in obese children (Chrzanowska *et al*., 2011). Leptin in obese subjects was inversely correlated with creatinine levels (Gray *et al*., 2014). Furthermore, involvement of leptin in obesity has been linked recently to leptin that may control the autonomic functions through dorsomedial hypothalamus (Kurajoh *et al*., 2015).

Increased level of leptin, considered as a marker of leptin resistance is noticed in obesity and cardiovascular disorders and represents an important diagnostic and therapeutic target for obesity disorders related to cardiovascular disease via interaction of leptin resistance with the metabolic and inflammatory factors (Martin *et al*., 2008). Leptin in obese subjects was positively correlated with HDL-cholesterol (Gray *et al*., 2014).

Inhibition of leptin maintains the stability of lean body, skeletal and adipose tissue masses, and the insulin lipogenic action is suppressed by obesity induced hyperleptinemia whereas insulin sensitivity and parasympathetic anabolic actions are enhanced by weight loss induced hypoleptinemia (Borer 2014). It was revealed that developmental programming disorders can lead to serious metabolic disorders and obesity (Vikers, 2007).

To understand the potential uses, significance, pathophysiology and precise relationship of leptin with obesity, it was reviewed thoroughly (Farr *et al*., 2015) through different angles for the role and efficacy of leptin in obesity. This review was carried out with the previous information that leptin can not induce weight loss and is effective only in combination with other therapies in causing weight loss (Farr *et al*., 2015). It was concluded that leptin might be efficacious in leptin deficiency induced obesity though the mechanisms of leptin resistance are still not clearly known to understand the role of leptin in obesity (Farr *et al*., 2015).

Preventing diet induced obesity by long term administration of voglibose (VO) in mice caused reduction in body weight, energy intake and fat mass, and leptin indicating that VO is potentially important for therapeutic use for the management of patients with obesity and diabetes type 2 (Do *et al*., 2014). A study carried out in rat shows that maternal high-fat diet during whole period of gestation and suckling influence the leptin sensitivity and obesity in offspring (Sun *et al*., 2012).

Serum level of leptin-the satiety-enhancing hormone in older subjects was linked to fat mass and obesity associated gene (FTO) (Benedict *et al*., 2014). Role of leptin in energy expenditure, regulation of food intake and obesity-associated atherosclerosis and cardiovascular disorders have been explained but another study revealed that plasma leptin levels and the leptin/soluble leptin receptor ratio were found associated with atherosclerosis in type 2 diabetic patients treated with insulin, but these associations were found independent of either obesity or other cardiovascular risk factors (Yamazaki *et al*., 2013).

Overweight/ obese women subjects showed higher leptin levels as compared to normal-weight women subjects and the leptin levels were associated with the total body fat (Ozias *et al*., 2014). Serum leptin was found strongly and positively correlated with BMI and calculated body fat percentage (Mohammadzadeh and Zarghami, 2013). Leptin in obese subjects was positively correlated with c-reactive protein (Gray *et al*., 2014).

It was found that the mean serum levels of leptin in type 2 diabetes mellitus patients were significantly higher than that of healthy controls (Mohammadzadeh *et al*., 2013). Plasma leptin level decreased with the administration of tofogliflozin- a highly selective sodium/glucose cotransporter 2 inhibitor that reduces the body weight in obese and diabetics type 2 subjects (Suzuki *et al*., 2014). Leptin is involved in obesity related disorders or other disorders in obese people e.g. T2DM, cardiovascular disorders, neurodegenerative disorders that indicates a communication between CNS and periphery (Forny-Germano *et al*., 2019).

Inspite of much research, we still have limited knowledge of the mechanisms whereby the resistance of the action of a metabolic hormone leptin occurs in obesity, and what strategies can lead to slow down the progression of obesity (Cui *et al*., 2017).

ADIPONECTIN AND OBESITY

Lower concentration of adiponectin was obtained in obese children (Chrzanowska *et al*., 2011). Adiponectin in obese subjects was not negatively correlated with body mass index (Gray *et al*., 2014). No significant correlations could be analyzed between adiponectin and any measure of the body composition (Ozias *et al*., 2014). Obesity was a stronger risk factor for decreased adiponectin among blacks than among whites or Hispanics (Gardener *et al*., 2013).

Serum adiponectin correlated negatively with BMI in normal subjects (Abdelgadir *et al*., 2013). Adiponectin was found lower in obese than non-obese subjects (Al-Hamodi *et al*., 2014). A non-significant decrease of adiponectin in obese subjects was obtained (Najam *et al*., 2014). The High fat low carbohydrate (HFLC) group showed greater mean increases in total adiponectin relative to the LFHC in obese subject groups (Ruth *et al*., 2013). Association between adiponectin and BMI varied in different race-ethnic groups (Gardener *et al*., 2013).

It has been suggested that adiponectin could play a significant role in the treatment and prevention of obesity and diabetes. The serum levels of adiponectin are higher in women and people with normal body weight, and lower in people with diabetes (Ostrowska *et al*., 2013).

Altered adiponectin signaling in obesity may lead to congnitive discomfort and Alzheimer's disease that indicates the role of adiponectin in the diagnostic and therapeutic aspects of in brain diseases (Forny-Germano *et al*., 2019). Functional regulation and significant role of adiponectin as a potential therapeutic target/ replacement therapy have been found for the management of obesity, insulin resistance, T2DM, atherosclerosis and other cardiovascular diseases (Achari and Jain, 2017). Subjects with AA genotype of rs2805533 comprised greater abdominal circumference, lower adiponectin level relative to those in AG and GG genotypes. This shows that adiponectin level is one of the intermediary major factors whereby genetic factors regulate obesity (Oguro *et al*., 2012).

LEPTIN AND DIABETES MELLITUS

Plasma adipokines (leptin and adiponectin) levels in type 1 diabetic subjects showed significantly higher leptin level but no difference in adiponectin level (Iacobellis *et al*., 2014). The serum leptin levels were significantly higher and adiponectin levels lower in diabetic dogs than those in healthy control dogs (Kim *et al*., 2015). Association of Leptin and adiponectin in type 2 diabetes mellitus for obese versus non-obese subjects provides interesting information in the pathophysiology of diabetes mellitus (Chearskul *et al*., 2015).

Enough information is available to link the pathogenesis of diabetes mellitus with the adipocyte leptin/ hypothalamus axis (Kalra 2009). Leptin is involved in diabetes (Veniant and LeBe, 2003; Fatima *et al*., 2017b) and leptin used for leptin deficiency conditions shows remarkable effects on insulin resistance, appetite and body weight (Veniant and LeBe, 2003). Leptin plasma levels and their relationship with insulin resistance in subjects with family history of type 2 diabetes (diabetes mellitus and normal glucose tolerant first degree relatives) were determined and adjusted for age and BMI that showed significantly higher leptin levels in diabetes mellitus and normal glucose tolerant first degree relatives than those in normal controls (Ren *et al*., 2010). Obese girls with insulin resistance gave a higher concentration of leptin comparing to obese girls without insulin resistance (Chrzanowska *et al*., 2011).

Literature review shows that the leptin levels in diabetic children wherein good metabolic control was planned were similar to those of healthy children, whereas, children with IDDM had higher leptin than non diabetic children in certain other studies; that might had been due to intensified insulin therapy causing chronic hyperinsulinemia with high levels of leptin (Verrotti *et al*., 2000). Subjects with Type 1 diabetes showed significantly higher plasma levels of leptin than control subjects (Iacobellis *et al*., 2014). Increased plasma leptin and epicardual fat was investigated in type 1 diabetes independently of obesity (Iacobellis *et al*., 2014).

Leptin was found significantly decreased in patients with poorly controlled DM type 2 than in well-controlled diabetics (Gu *et al*., 2014). Leptin serum level in type 2 diabetics was found significantly lower than that in non-diabetic controls (Mohammadzadeh and Zarghami, 2013). Leptin correlating positively with age, waist and BMI in normal glucose tolerant first degree relatives explains the possible genetic defects of leptin in the development of familial type 2 diabetes (Ren *et al*., 2010).

Brain neurons and neurotransmitters mediating leptin action influence the leptin to restore euglycemia in fasting via neurocircuity and peripheral pathways that may provide the understanding for specific novel targets for insulin independent therapeutics against T1DM (Xu and Tong, 2017).

It has been found that polymorphism of the leptin receptor gene associates with macroangiopathy in type 2 diabetes mellitus and is associated with increasing plasma leptin that could serve as a useful predictive marker in diabetic macroangiopathy (Gan and Yang, 2012). Serum leptin enhancing susceptibility in response to infections in patients with diabetes was managed by vitamin D supplementation possibly to change leptin and other adipokines in type 2 diabetes (Ghavamzadeh *et al*., 2014). The results showed significant efficacy of vitamin D supplementation in preventing diabetic complications (Ghavamzadeh *et al*., 2014).

Hyperleptinemia due to energy rich diets inhibits the transport of leptin across blood brain barrier and hence, leptin insufficiency in hypothalamus occurs resulting into the loss of hypothalamus restraint on the secretion of pancreatic insulin leading to diabetes type 1 and type 2 (Nakano *et al*., 2012). It has been noted that Leptin is independently associated with the insulin resistance and is involved in obesity (Martin *et al*., 2008) may modulate insulin resistance in the cell membrane (Wang *et al*., 2013a).

Leptin levels are related with micro/macrovascular diabetic disorders, insulin resistance and T2DM and these metabolic hormones are influenced by antidiabetic drugs that emphasize to think about using leptin as a therapeutic target for diabetes and other diseases (Katsiki *et al*., 2018). Furthermore, obesity induced leptin resistance causes injuries in myocardium, liver, vasculature, platelets, pancreas etc., and injuries related to metabolic and inflammatory processes may occur due to leptin resistance in certain tissues or increased action of hyperleptinemia (Martin *et al*., 2008).

It was suggested that either defective leptin production or secretion or both the defective production and secretion of leptin not depending on metabolic control occur in female T1DM and T2DM (Roden *et al*., 2000) confirmed by a study showing the leptin levels lower in T1DM and T2DM compared to that in non-diabetics. Leptin is associated in patients with T1DM via albuminuria and nephropathy (Bulum *et al*., 2019).

ADIPONECTIN AND DIABETES MELLITUS

Hypoadiponectinemia was found to be connected with insulin resistance (Chrzanowska *et al*., 2011). Whereas no differences were present in adiponectin between subjects with diabetes type 1 and control subjects (Iacobellis *et al*., 2014). Adiponectin in obese subjects was negatively correlated with insulin (Gray *et al*., 2014). Lower levels of adiponectin levels were found in diabetic subjects (Gardener *et al*., 2013). Adiponectin levels were significantly lower in type 2 diabetics while compared with controls (Abdelgadir *et al*., 2013). It has been suggested that low serum levels of adiponectin could be a factor of diabetes type 2 in obese Korean children (Oh *et al*., 2012). Significant decreased serum levels of adiponectin were obtained in T2DM subjects compared to non-diabetic control subjects (Najam *et al*., 2014). Adiponectin levels were lower in Trinidadian type 2 diabetic subjects (Nayak *et al*., 2012).

Adiponectin was found higher in patients with normoalbuminuria compared with microalbuminuria patients with T1DM. Association of adiponectin with diabetes type 2 has been discussed (Hossain *et al*., 2015). Adiponectin levels are linked to insulin sensitivity independently of BMI, though the race specific regulating mechanisms or certain different type 2 diabetes phenotype might provide explanation for type 2 diabetes in Sudanese subjects (Abdelgadir *et al*., 2013). The mean adiponectin levels significantly varied among ethnic groups in Trinidadian type 2 diabetic (Nayak *et al*., 2012). Adiponectin levels associate with better glycemic control and hence, its increased levels might serve as diagnostic marker and control of insulin resistance (IR) and T2DM (Abdella and Mojiminiyi, 2018).

Adiponectin correlated positively with glucose serum levels in diabetic group (Abdelgadir *et al*., 2013). Lower levels of adiponectin levels were found in subjects with increased BMI (Gardener *et al*., 2013). Adiponectin did not

correlate with leptin in diabetic group (Abdelgadir *et al*., 2013). The serum level of adiponectin are higher in women and people with normal body weight, and lower in people with diabetes (Ostrowska *et al*., 2013). Male and female comparison for adiponectin levels did not show significance in diabetic as well as control groups (Abdelgadir *et al*., 2013).

It was found that variations in genes encoding adiponectin (ADIPOQ), but not its receptors (ADIPOR1/R2) were associated with the altered level of adiponectin, though the ADIPOQ and its receptors are not involved in causing the risk of insulin resistance. However, ADIPOQ and its receptors are associated with diabetes type 2 in European-Australians (Peters *et al*., 2013).

DIABETES MELLITUS, OBESITY AND ADIPOKINES

There is a link among diabetes, obesity and leptin though more studies are needed to determine the existing biological mechanism (Farkhondeh *et al*., 2019). Association of Adiponectin and leptin in obese T1DM showed significant decrease than in non-obese T1DM patients (Musil *et al*., 2015). Whereas the association of adiponectin and leptin increased transiently immediately after fasting (Musil *et al*., 2015).

Adipokines have been considered as the main dysmetabolic biomarkers in overweight, obese and diabetic subjects; and has been suggested as potentially significant in diagnosing the cardiovascular and diabetes mellitus type 2 risk in overweight and obese patients (Benbaibeche *et al*., 2014).

Musil *et al*. (2015) determined the levels of adipokines in obese type 1 diabetes and influence of reduction in body weight on plasma levels of leptin and association between leptin and adiponectin in these patients. It was concluded that obese DM type 1 patients are characterized by hyperleptinemia that is decreased by prolonged fasting, but only little affected by low calorie diet (Musil *et al*., 2015).

LEPTIN, DIABETES MELLITUS AND OBESITY

Much work has been carried out for understanding the cellular and molecular mechanisms for leptin resistance in diabetes mellitus influencing neuroendocrine regulation of energy homeostasis and obesity (Cui *et al*., 2017). Increased leptin levels are better indicator of the effect of obesity in diabetic retinopathy in T2DM (Afarid *et al*., 2018).

Plasma leptin level in obese T1DM was found significantly higher than in non-obese T1DM subjects (Musil *et al*., 2015). Plasma leptin concentrations in type 2 diabetes overweight patients were found associated with the vascular endothelial function (Morioka *et al*., 2014). Review comparisons indicate that mean levels of leptin in obese diabetics (IDDM) were significantly higher compared to those in non-obese diabetic patients (IDDM) (Verrotti *et al*., 2000). Insulin and leptin fasting levels were measured in obese and non-obese subjects with a family history of type 2 diabetes that showed fasting leptin and insulin levels significantly higher in obese compared to non-obese control subjects (Fluitt *et al*., 2013). Hyperleptinemia can influence the cardiac autonomic dysfunction in patients having diabetes type 2 and visceral obesity (Kurajoh *et al*., 2015).

Efficacy of leptin replenishment in vivo has been documented with gene therapy and by preventing hyperinsulinemia, hyperglycemia and insulin resistance for diabetes type1 and 2 with or without obesity (Kalra 2009). It has been proposed (Nakano *et al*., 2012) that leptin gene therapy could be helpful in reducing the epidemic of obesity, and diabetes worldwide that can also help managing the shortened life span. A significant correlation for decrease in leptin and less risk of no improvement in insulin resistance; and a moderate reduction in body weight in obese subjects accompanying improvement in insulin resistance and decrease in serum leptin, were found (Wang *et al*., 2013).

Gu *et al*. (2014) determined the serum leptin concentration in obese women patients with and without diabetes mellitus. Al-Hamodi *et al*. (2014) carried out a series of investigations and found higher leptin in non-obese type 2 diabetics; and positive correlation of leptin with BMI. Positive correlation of leptin only with BMI and HDL-C was determined in obese women without diabetes mellitus type 2 (Gu *et al*., 2014). Plasma leptin level decreased transiently immediately after fasting (Musil *et al*., 2015). Verrotti *et al*. (2000) reviewed the literature and their analysis showed that the leptin levels in children with diabetes type 1 were similar to those in healthy obese subjects. A study carried out to understand whether leptin influenced by cardiopulmonary bypass are dependent on diabetes and insulin, interleukin-6, high sensitivity c reactive protein and cortisol, it was found that the acute phase response differs by higher leptin levels in diabetics independent of gender, BMI, and the levels of interleukin-6, insulin, high sensitive CRP and cortisol (Guvener *et al*., 2012). Survey of literature explains that the serum leptin levels declined in obese diabetic subjects during weight loss. Leptin was significantly decreased in the group of obese women with diabetes type 2 than in group of obese women without diabetes mellitus type 2 (Gu *et al*., 2014).

It was characterized that the factors most strongly predictive of low insulin sensitivity were body mass index, and high plasma leptin levels; and on that basis, leptin signaling may be significant early contributor in the

pathogenesis of type 2 diabetes at this disease stage equally or more important than low-grade inflammation and ectopic lipids (Rottenkolber *et al*., 2015).

Leptin is involved in the pathogenesis of diabetes type 2 and obesity. Variations in leptin levels in non-obese subjects with diabetes type 2 showed that the lower serum leptin levels obtained in diabetic patients may be a result of male gender as serum leptin level in women is influenced differently than that in men (Mohammadzadeh and Zarghami, 2013).

Leptin increases in obesity and diabetes and it is considered as mediating insulin sensitivity in hepatocytes whereby the mechanism for increase in body fat mass leading to insulin resistance in diabetes type 2 can be explained. However, another potential change found in both obese and diabetic type 2 subjects is oxidative stress (Pandey *et al*., 2015). Hence, the variations in leptin may be quite informative in connection with the occurrence of oxidative stress. These results provide information that not only leptin but oxidative stress is another predictor in understanding the obesity and diabetes type 2 (Pandey *et al*., 2015).

Omeprazole and exendin-4 in combination reduce food intake and body weight gain in experimental mice model of obesity and type 2 diabetes, and one of the potential factor involved in bringing this change might be leptin (Patel *et al*., 2013). It has been suggested that hyperleptinemia and visceral fat accumulation are at least partly due to decrease in brain-derived neurotrophic factor (BDNF) in ventromedial hypothalamus (VMH) primarily caused by impaired glucose utilization in experimental rats (Maekawa *et al*., 2013). This provides an evidence that BDN could be an effective and potential treatment of leptin resistance, hyperleptinemia and visceral obesity in type 2 diabetic patients (Maekawa *et al*., 2013). Mutation in lep gene decreases the leptin blood levels and causes obesity and T2DM, and fasting and related behaviour can hence, serve as treatment for obesity and T2DM (Qadir and Ahmed, 2017).

ADIPONECTIN, DIABETES MELLITUS AND OBESITY

Adiponectin levels did not vary between non-obese type 2 diabetics and controls (Al-Hamodi *et al*., 2014). Adiponectin in both non-obese and obese groups associated independently with family history of diabetes (FHD) (Oh *et al*., 2012). It was concluded that adiponectin is not influenced by the effects of diabetes. i.e. adiponectin changes in diabetes type 2 may be because of obesity and could be an important factor linking with type 2 diabetes, insulin resistance and adiposity (Al-Hamodi *et al*., 2014). Thai obese adults having diabetes type 2 showed higher ratios of leptin/adiponectin, and more incidences of cardiometabolic risk including hypertension and hypertriglyceridemia as compared in non-obese subjects with diabetes type 2 (Chearskul *et al*., 2015). Adiponectin negatively correlated with waist circumference in obese non-diabetic subjects and non-obese type 2 diabetic patients (Al-Hamodi *et al*., 2014). Serum adiponectin in subjects with family history of diabetes (FHD) significantly decreased than those without family history of diabetes (FHD) in both non-obese and obese groups (Oh *et al*., 2012).

Adiponectin negatively correlated with BMI in obese non-diabetic subjects and non-obese type 2 diabetic patients (Al-Hamodi *et al*., 2014). Adiponectin correlated negatively with leptin in obese non-diabetic subjects and non-obese type 2 diabetic patients (Al-Hamodi *et al*., 2014). Adiponectin correlated negatively with leptin/ adiponectin ratio in obese non-diabetic subjects and non-obese type 2 diabetic patients (Al-Hamodi *et al*., 2014). Hypertension, low HDL-C, triglycerides associated strongly with low adiponectin in subjects that were not obese than those who were obese (Gardener *et al*., 2013). Adiponectin negatively correlated with insulin in obese non-diabetic subjects and non-obese type 2 diabetic patients (Al-Hamodi *et al*., 2014). No significant gender based change could be found in adiponectin levels in diabetic and obese patients (Najam *et al*., 2014).

Instead of frequent intake of terrestrial meats, the frequent use of lean seafood increases the insulin sensitizing hormone adiponectin and decreases energy intake and hence, prevents from obesity, insulin resistance, and T2DM, though it needs further investigations to establish the dietary influence of energy intake/ energy balance on obesity and insulin resistance leading to T2DM (Liaset *et al*., 2019).

CONCLUSIONS

Weight loss targets/ programs can be established by the important role of nurse practitioners in clinical practice since they have in-depth awareness of the research in diverse aspects of obesity/ weight management. Various human diseases including obesity and diabetes are linked with the intestinal microbiota. Furthermore, overweight and obese conditions are alarming risk factor for most of the T2DM patients that requires the implementation of better primary care and all possible strategies.

A variety of behavioral, physiological and physiochemical alterations may occur in patients with diabetes. However, the best way to uncover the newer and important aspects of this disease is to determine, analyze and correlate the factors which may be interacting with each other and are involved some way in the pathophysiological processes leading to disordered conditions. In other words, multidisciplinary approach of investigating the causes

and effects, their precise interactions, observing and interpreting the diagnostic features, and therapeutic management might provide us more knowledge of multifactorial diseases like diabetes.

Although there are a variety of factors at clinical, physiological, cellular and molecular level that are considered important in diabetology, present review describes the studies for elucidating the precise role of these factors in diabetes mellitus. However, further more detailed studies are required to understand the impact and role of these and related variables in the Pathophysiology of diabetes mellitus.

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