International Research Journal of Medicine and Biomedical Sciences Vol.4 (1),pp. 8-12, January 2019
Available online at http://www.journalissues.org/IRJMBS/
https://doi.org/10.15739/irjmbs.19.002

ISSN 2488-9032

Review

Pathophysiology of metabolic syndrome-The role of central obesity

Received 23 November, 2018 | Revised 13 January, 2019 | Accepted 23 January, 2019 | Published 28 January, 2019

***Odoh G[1], Uwakwe JN[1]**
Edah JO[1], Ojobi JE[2]
and
Chuhwak EK[1]

[1]Department of Internal medicine, Jos University Teaching Hospital, Jos, Nigeria.
[2]Department of Internal Medicine, Federal Medical Center Markudi.

*Corresponding Author
Email: gabrielodoh@gmail.com

Tel.:+2348034947611

The term Metabolic Syndrome (MetS) refers to the clustering of a number of cardiovascular risk factors: obesity (usually central), hypertension, dyslipidaemia, glucose intolerance, prothrombotic state and inflammation. MetS is a predictor of type 2 diabetes mellitus and cardiovascular disease. Jean Vague in the 1940s and early 1950s related the presence of male type (android form) of adiposity to the development of diabetes mellitus and cardiovascular diseases which are all important factors of the MetS. MetS is defined based on a variety of criteria, such as the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), World Health Organization (WHO) and International Diabetes Federation (IDF) .Central obesity is an important component of MetS in these definitions. This is largely due to the key role played by the adipocyte in the development of the syndrome. The contents of this article were drawn from an extensive online search of literature covering the subject matter, and aims to review the pathophysiological role of central obesity in the development of the components of the metabolic syndrome.

Key words: Obesity, diabetes mellitus, cholesterol, cardiovascular risk.

INTRODUCTION

The awareness of the health community to the metabolic syndrome was stimulated by Raeven (Raeven, 1988) in his Banting Lecture, observed how dylipidaemia, hypertension and hyperglycaemia cluster in the same individuals. He called this clustering "Syndrome X" and emphasized its role as a risk factor for cardiovascular disease. Reaven did not include abdominal obesity in his original definition of MetS (Eckel et al., 2005). Although the concept of MetS became more popular by Reaven's Lecture, concepts similar to the MetS have been variously described in the past. Kylin in the 1920s described the clustering of hypertension, dyslipidaemia and gout in the same individuals (Kylin, 1923). Two to three decades later, Jean Vague in the late 1940s and early 1950s, in his paper on special sexual differentiation of obesity, noted that upper body adiposity (android or male type adiposity) was most often associated with metabolic abnormalities associated with diabetes mellitus and cardiovascular diseases. He later called this association "diabetogenic obesity" (Vague, 1947). This description of obesity fits into what is referred today as central obesity. (Haller, 1977) was the first to use the term "Metabolic syndrome" in describing the association between obesity, diabetes mellitus, hyperlipoproteinaemia, hyperuricaemia and hepatic steatosis (Singer, 1977; Phillip,

1978; Phillip, 1978) also described the association of obesity with other risk factors that predispose to cardiovascular disease and diabetes mellitus.

Some of the recent definitions of the MetS include those of the World Health Organization (WHO) (Alberti and Zimmet, 1998), The National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP III) (NCEP, 2002) and that by the International Diabetic Federation (IDF) (Albertis et al., 2005). The World Health Organization (WHO, 1998) definition, requires the presence of insulin resistance and /or impaired glucose tolerance / diabetes, with any two of the following: central obesity, waist to hip ratio of >0.9 (in men) or 0.85 (in women) and/or BMI of ≥30kg/m^2, triglycerides ≥1.7mMol/L and/or low HDL-cholesterol (<0.9mMol/L in men and <1mMol/L in women), arterial blood pressure of ≥140/90 mmHg and microalbuminuria. The National Cholestesterol Educational program Adult Treatment Panel III (NCEP ATP III) defined MetS by the presence of any 3 of the following; hypertension (> 130/85 mmHg), dyslipidaemia (HDL-C < 1.0 mmol/L and/or triglycerides > 1.7 mmol/L) and abdominal obesity (waist circumference of 102cm in men and 88cm in women).

The International Diabetes federation definition of MetS requires the presence of central obesity (waist circumference of ≥ 94cm in men and ≥ 80cm in women amongst Europeans and Africans) and any two of the following; fasting plasma glucose ≥5.6mmol/L (or a diagnosis of diabetes mellitus), serum triglycerides of ≥1.7mmol/L, HDL of <1.0 mMol/L in men and <1.3 mMol/L in women, and blood pressure of ≥130/85mmHg (or an existing diagnosis of hypertension).

Obesity, from the definitions above, is key in the definition for MetS. This article will therefore try to review the role of abdominal obesity in the pathophysioloy/pathogenesis of the various components of MetS.

Pathogenesis of metabolic syndrome

Advances in adipocyte biology, sub-clinical inflammation, and oxidative stress have added to how the initial understanding of obesity and insulin resistance contribute to metabolic syndrome (Dandona et al., 2005). Abdominal fat content, determined by waist circumference and waist to hip ratio has shown strong correlation with insulin resistance, prothrombotic factors, inflammation, hypertension, dyslipidaemia and hyperglycaemia (Ahima and Flier, 2000) which are the core components of the metabolic syndrome. Whether individual component of the metabolic syndrome have a common originating pathology or represent an independent or unique pathology is still contentious. However, visceral (central) obesity has been reported to be the primary initiating factor for most of the pathways involved in development of the components of the metabolic syndrome (Matsuzawa et al., 2011).Visceral fat deposit (as demonstrated by waist circumference) contributes more to insulin resistance than subcutenous fat (peripheral fat), because it is more resistant to the action of insulin and more sensitive to lipolytic hormones, which increase release of free fatty acids (FFAs) (John, 2006). The increase FFAs serve as substrates for the synthesis of triglycerides and small dense atherogenic LDL particles[15] which are the basic lipid abnormalities of the MetS . Insulin resistance is greater in individuals with predominantly visceral fat acccumulation than in those with subcutaneous fat accumulation because lipolysis of visceral fat content leads to increase supply of FFA via the splanchnic circulation to the liver. The released FFAs directly inhibits the action of insulin on its receptors (Bulcão et al., 2006; Kong et al., 2006). Abdominal obesity (visceral fat) also contributes to insulin resistance by decreasing adiponectin levels[17]. Normal adiponectin levels increases insulin sensitivity and is anti-inflammatory. Hence, decreased levels of adiponectin in abdominal obesity further worsen insulin resistance and predispose to pro-inflammatory state. Abdominal obesity also leads to increased secretion of interleukin-6 (IL-6), tumour necrosis factor- alfa (TNF-α) and C-reactive protein (C-RP). These three chemical mediators lead to an increased inflammatory state which further worsens insulin resistance. Obesity also enhances the activity of the endocannabinoid system, leading to stimulation of the appetite centre in hypothalamus; this lead to weight gain, worsening obesity and aggravating insulin resistance (Pagotto et al., 2006).

Effects of insulin resistance

Insulin resistance which results from abnormalities of central obesity is mediated via increase in circulating FFAs. It is believed to play a very important role in the pathogenesis of MetS. Physiologically, insulin mediates increase glucose uptake in muscle and liver, inhibits lipolysis and mediates inhibition of hepatic gluconeogenesis. Insulin resistance in adipose tissue impairs insulin mediated inhibition of lipolysis, leading to increase FFAs that further inhibit the anti-lipolytic effect of insulin (Boden and Shulman, 2002). The enhanced lipolysis leads to the formation of FFAs which inhibit protein kinase activation in muscles cell, reducing glucose uptake and predisposing to hyperglycaemia. Decreased protein kinase activation in the liver promotes gluconeogenesis and lipogenesis. The resulting hyperglycaemia from above abnormalities results in the creation of compensatory hyperinsulinaemic state to maintain euglycaemia. Eventually the compensatory response fails and insulin secretion decreases, leading to sustained hyperglycaemia, which is an important component of MetS. The free fatty acids (FFAs) are also lipotoxic to β -cells of islets of langerhans, further reducing insulin secretion (Tooke and Hannemann, 2000), and leading to worsening the hyperglycaemia. Hence the release of FFA induces hyperglycaemia by causing insulin resistance and β-cell secretory defect.

Insulin resistance also contributes to the development of hypertension, another core component of MetS due to the

loss of vasodilator effect of insulin and vasoconstriction caused by FFAs. This is due to the fact that insulin reduces sympathetic nerve stimulation which is a trigger for vasoconstriction (Tripathy et al., 2003). Other contributing mechanisms to the development of hypertension include: sympathetic activation and increased sodium re-absorption by the kidneys secondary to hyperinsulinaemia. Furthermore, insulin resistance causes increased serum viscosity, induction of prothrombotic state and release of pro-inflammatory cytokines from adipose tissues which contribute to increase risk of cardiovascular disease (Juhan-Vague et al., 2003)

Neurohormonal activation

Further understanding of endocrine and immune properties of adipocytes have provided better insight into the mechanism of development of MetS. Adipokines released from visceral tissues have been shown to be associated with MetS and cardiovascular disease (Wallace et al., 2001). Leptin is an adipokine that controls energy homeostasis mediated by the hypothalamus. Obesity is associated with increased leptin levels and higher leptin levels are directly correlated to increase cardiovascular risk. Adiponectin is anti-inflammatory and anti-atherogenic adipokine. It decreases both vascular reactivity, smooth muscle proliferation and promotes plaque stability

(Lindsay et al., 2002). Adiponectin has been considered a protective factor against the development of diabetes, hypertension and myocardial infarction (Ouchi et al., 2003; Pischon et al., 2004) Adipose tissue mass (abdominal obesity) has inverse correlation with adiponectin levels but positively correlated with leptin levels. These two factors are known to promote plaque instability, smooth muscle proliferation and vascular reactivity, all of which increase the risk of adverse cardiovascular events. Decrease adiponectin levels as explained earlier will predispose to development of hypertension and diabetes mellitus, which are major cardiovascular risk factors and also very important components of the metabolic syndrome. Activation of the Renin-angiotensin-system (RAS) also serves as an important neurohormonal pathway contributing to the MetS. Angiotensin II is a hormone formed as a result of angiotensin converting enzyme activation and is also secreted by the adipose tissue. Obesity and insulin resistance are associated with increase production of angiotesin II (Vanecková et al., 2014). Angiotesin II through activation of the type 2 receptor, activates Adenine-Dinucleotide phosphatidase leading to generation of reactive oxygen species (ROS) (Mehta and Griendling, 2007). Reactive oxygen species precipitate a multitude of effects including oxidation of LDL, endothelial injury, platelets aggregation, expression of redox sensitive transcription factor; nuclear kappa light chain enhancer or activated β cells (NF-Kβ) and expression of lecithin –like oxidized low density lipoprotein-1(Lox-1) on the endothelium and vascular smooth muscle cells (Gobal et al., 2011). The RAS, ROS, and LOX-1 have an interrelated positive feedback loop that initiates vicious cycle of inflammation, endothelial damage, fibroblast proliferation; that contribute to development of hypertension, diabetes, cardiac hypertrophy and CVD (Dai et al., 2013).

The effect of inflammation

Activation of the various pro-atherogenic pathways results in inflammation that eventually leads to clinical manifestation of MetS. As explained earlier, systemic oxidative stress induced by central obesity and insulin resistance leads to increase activation of further signals cascade culminating to atherogenesis and fibrosis. Inflammation plays a cardinal role in the evolution of CVD and various inflammatory markers (Pant et al., 2014) and has been shown to be increased in MetS; whether the markers play a causative role or are mere by-standers of ongoing inflammation remains controversial. Below are some of the roles played by the inflammatory markers.

Tumor Necrosis Factor alfa (TNF-α)

Macrophages within adipose tissues secretes TNF-α and its production increase with in increasing adipose tissue mass. Tumour Necrosis factor alfa causes phosphorylation and inactivation of insulin receptors in adipose tissue as well as in smooth muscle, and also the induction of lipolysis leading to increase FFA and inhibition of adiponectin release (Hotamisligil et al., 1994), decrease adiponectin leads to plethora of effects explained earlier. Elevation of TNF α-1 is associated with obesity and insulin resistance both of which are major component of MetS (Tsigos et al., 1999).

Interleukin-6 (IL-6) and C-Reactive Protein (CRP)

Interleukin-6, a cytokine produced by adipocytes and immune cells, plays a key role in the pathophysiology of MetS (Fried et al., 1998). Production of IL-6 increases with increased body fat and insulin resistance. It acts on the liver, bone marrow, and endothelium; leading to increased production of acute phase reactants from the liver such as C-Reactive Protein (CRP). A study by Bastard et al (Bastard et al., 2000) demonstrated a positive correlation between high CRP levels and development of MetS, diabetes mellitus and CVD .

Interleukin-6 also increases fibrinogen levels resulting in pro-thrombotic state. Interleukin-6 also promotes adhesion molecule expression by endothelial cells and activation of RAS pathway (Wisse, 2004). Other contributing factors to the development of metabolic syndrome include.

Stress

Studies indicate that stress can be an underlying cause of MetS by upsetting hormonal balance of hypothalamo-pituitary-adrenal axis (HPA) axis (Tsigos and Chrousos, 2002) causing high cortisol levels which raises glucose and insulin levels. This leads to insulin mediated effect on

adipose tissue. As explained earlier, visceral fat disorders can predispose individuals to insulin resistance, dyslipidaemia and hypertension(Rosmond and Bjorntop, 2000).

Sedentary life style

Sedentary life style has also been associated with the syndrome. Compared to individuals that watch television or videos or use computer for less than an hour a day, those that carry out this behaviour for more than 4 hours daily have a 2 fold increased risk of developing the MetS (Fanci and Anthony, 2008). Sedentary life style is also associated with obesity which is a major component and also a precursor to other components as discussed earlier.

CONCLUSION

Central Obesity (abdominal obesity) is the single most important precursor of all the components of the metabolic syndrome.

We advocate for early detection of central obesity, by simple measures such as the use measuring tape to assess the waist circumference. And interventions, usually life style modifications (dietary modification and exercise) which are usually cheap and very effective, will go a long way in preventing/ retarding the components of the MetS and their attendants' morbidity and mortality.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of the paper.

REFERENCES

Ahima RS, Flier JS(2000). Adipose tissue as an endocrine organ. J Clin Endocrinol Metab.11(8):327-332. 321.

Alberti KG, Zimmet PZ (1998). Definition, Diagnosis and classification of diabetes mellitus and its complications part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet. Med.15 (7):539-553.

Albertis KG, Zimmet P, Shaw JE. IDF (2005). Epediomology Task Force Consensus Group; Metabolic syndrome, a new world definition Lancet 366(9491):1059- 1062.

Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B (2000). Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab. 85(9): 3338–3342.

Boden G, Shulman GI (2002). Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur. J. Clin. Invest 32(Suppl. 3): 14–23.

Bulcão C, Ferreira SR, Giuffrida FM, Ribeiro-Filho FF(2006). The new adipose tissue and adipocytokines. Curr Diabetes Rev. 2(1):19-28.

Dai Y, Mercanti F, Dai D, et al.; LOX-1, a bridge between GLP-1R and mitochondrial ROS generation in human vascular smooth muscle cells. Biochem Biophys Res Commun 2013; 437(1): 62–66.

Dai Y, Mercanti F, Dai D, Wang X, Ding Z, Pothineni NV, Mehta JL (2014). Inflammation and Atherosclerosis – revisited. J Cardiovasc Pharmacol Ther 19(2): 170–178.

Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R (2005). Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation.111(11):1448-1454.

Eckel RH, Grundy SM, Zimmet PZ(2005). The metabolic syndrome Lancet; 265:1415-1428.

Fanci, Anthony S(2008). Harrison's principles of internal medicine. McGrew-Hill medical. ISBN 0-07-147692-X.

Fried SK, Bunkin DA and Greenberg AS(1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 83(3): 847–850.

Gobal F, Deshmukh A, Shah S, Mehta JL (2011). Triad of metabolic syndrome, chronic kidney disease, and coronary heart disease with a focus on microalbuminuria: death by overeating. J Am. Coll Cardiol; 57(23): 2303–2308.

Haller H(1977). (E epidemiology and associated risk factors of hyperlipoproteinemia) German 2 Gerzamte inn med.; 32(8): 124-128.

Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM(1994). Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A 91(11): 4854–4858.

John W (2006). The Metabolic Syndrome: Early Clues, Effective Management. Meditmag. 2(5): 1-7.

Juhan-Vague I, Alessi MC, Mavri A, Morange PE(2003). Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost 1(7): 1575–1579.

Kong AP, Chan NN, Chan JC (2006). The role of adipocytokines and neuro-hormonal dysregulation in metabolic syndrome. Curr. Diabetes Rev.; 2(4):397-407.

Kylin E (1923). Studien uber das Hypertonie-Hyperglykamie- Hyperurikamiesyndrom. Zentrabl. finnere. Med. Leipz. 81:105–127.

Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J(2002).Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet; 360(9326): 57–58.

Matsuzawa Y, Funahashi T Nakamura T (2011). The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. J Atheroscler Thromb; 18(8): 629–639.

Mehta PK, Griendling KK (2007). Angiotensin II cell signaling: physiological and pathological Therapeutic Advances in Cardiovascular Disease 11(8) 224 http://tac.sagepub.com effects in the cardiovascular

system.
Am J Physiol Cell Physiol; 292(1): C82–C97.
Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, Kishida K, Maeda N, Nagasawa A, Kobayashi H, Hiraoka H, Komai N, Kaibe M, Rakugi H, Ogihara T, Matsuzawa Y(2003). Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension; 42(3): 231–234.
Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R(2006). The emerging role of the endocannabinoid system in endocrine regulation of energy balance. Endocr Rev. Feb 27(1):73-100. Epub 2005 Nov 23.
Philip GB (1978). Sex hormones, risks factors and cardiovascular disease. Am J Med.; 65:7-11.
Philips GB (1977). Relationship between sex hormones, glucose, insulin and lipid abnormalities in men with myocardiac infarction. Proct Natl Acad Sci USA. 74: 1729-1733.
Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB (2004). Plasma adiponectin levels and risk of myocardial infarction in men. JAMA; 291(14): 1730–1737.
Raeven GM(1988). Role of insulin resistance in human diseases. Diabetes; 37:1595-1607
Rosmond R, Bjorntop P (2000). "The hypothalamic-pituitary- adrenal axis activity as a predictor of cardiovascular disease, T2DM and stroke" J intern med. Feb; 247 (2): 188-197.
Singer PC (1977). (diagnosis of primary lipoproteinemia) German 2 Gerzamte inn Med. 32(9): 129-133.
Third Report of the National Cholesterol Educational Program (NCEP) 2002. Expert Panel on Detection, Evaluation and treatment of high blood Cholesterol in Adults (Adult Treatment Panel 111) final report. Circulation. 106(25):3143-3421.
Tooke JE, Hannemann MM(2000). Adverse endothelial function and the insulin resistance syndrome. J Intern Med 247(4): 425–431.
Tripathy D, Mohanty P, Dhindsa S, Syed T, Ghanim H, Aljada A, Dandona P(2003). Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. Diabetes 52(12): 2882–2887.
Tsigos C, Chrousos CP(2002). "Hypothalamic-Pituitary-adrenal axis, neuroendocrine factor and stress" J Psycosom Res October 53(4): 865-871.
Tsigos C, Kyrou I, Chala E, Tsapogas P, Stavridis JC, Raptis SA, Katsilambros N, (1999). Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. Metabolism; 48(10): 1332–1335.
Vague JV (1947). Sexual differentiation, a factor affecting the forms of obesity. Presse Med.; 30:339–340.
Vaněčková I, Maletínská L, Behuliak M, Nagelová V, Zicha J, Kuneš J (2014). Obesity-related hypertension: possible pathophysiological mechanisms. J Endocrinol 223(3): R63–R78.
Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N(2001). Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001; 104(25): 3052–3056.
Wisse BE(2004). The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J. Am. Soc. Nephrol; 15(11): 2792–2800.