Vol. 13(1), pp. 1-7, January-June 2023
DOI: 10.5897/JMLD2022.0174
Article Number: 5642CC270382
ISSN 2141-2618

http://www.academicjournals.org/JMLD

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Journal of Medical Laboratory and Diagnosis

Full Length Research Paper

Criteria for the diagnosis of metabolic syndrome: A review

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Received 30 December, 2022; Accepted 20 January, 2023

Metabolic syndrome (MetS) consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of cardiovascular events and type 2 diabetes (T2D). It confers 2-fold increase in relative risk for atherosclerotic cardiovascular events and 5-fold increase in risk for development of T2D as compared with people without the syndrome. T2D is one of the most prevalent and serious metabolic diseases in the world, and among middle-aged men CHD is still the leading cause of mortality in western countries. Definitions of MetS vary widely with experts resulting in inconsistent diagnosis and inappropriate management. Consistent definition of the MetS and its feature would facilitate research into its causes and may facilitate its treatment. This review made a critical assessment of the criteria and suggested a way forward. Literature search between 2000 and 2022 was conducted and 60 publications including the author's works were evaluated. From the review, it was established that both IR and obesity can give rise to all the risk factors and to each other. Therefore, if efforts are made to streamline the diagnosis of IR and obesity, there may not be need for the other varying specifications and criteria of universal application could emerge.

Key words: Metabolic syndrome, insulin resistance syndrome, glucose intolerance, hyperinsulinaemia, dislipidaemia, obesity, risk factors.

INTRODUCTION

Metabolic syndrome (MetS), also called Insulin Resistance Syndrome or Syndrome X or Dismetabolic Syndrome or Hypernutrition Syndrome (Titov 2014) consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of cardiovascular events and type 2 diabetes (T2D). It confers 2-fold increase in relative risk for atherosclerotic cardiovascular events and 5-fold increase in risk for development of T2D as compared with people without the syndrome (Grundy et al., 2005a). T2D is one of the most prevalent and serious metabolic diseases in the world, and among middle-aged men, CHD is still the leading cause of mortality in western countries. Smith et al. (2020) noted that MetS increases the risk severe viral infections also. MetS has reached a pandemic proportion and has an impact on the incidence and severity of cardiovascular pathologies (Chlup et al., 2004). It is a huge public health problem worldwide (Afar et al., 2018), that is responsible for a growing number of premature deaths throughout the world. Diagnosing MetS enables clinicians to identify patients at high risk for pressure, elevated plasma glucose, a pro-thrombotic and developing T2D and CVD

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and target them for more aggressive risk factor management and disease surveillance. The accuracy, consistency and uniformity of diagnosis depend on the criteria for the definition of the syndrome. Definition varies widely with experts, (Wang et al., 2020) resulting in inconsistent diagnosis and inappropriate management. Consistent definition of the MetS and its features would facilitate research into its causes and may facilitate its treatment. In this paper, the criteria for the definition and diagnosis of MetS are reviewed with a view to highlighting the key factors of the syndrome so that diagnosis could be facilitated.

LITERATURE REVIEW

Literature search was conducted as from 2000 through 2022 on such key words as “risk factors for metabolic syndrome”, “insulin resistance”, “insulin resistance syndrome”, “metabolic syndrome”, “atherogenic dyslipidaemia” and it yielded more than 500 articles. From these, 60 publications were reviewed including works by the author.

Pathogenesis of metabolic syndrome

The pathogenesis of MetS is thought to be multi-factoral and encompasses environmental and genetic factors. These factors include altered adipose tissue and adipocyte function (Kahn et al., 2019) oxidative stress and visceral obesity (Ahjoub and Massrou-Roudsari, 2012, Wang et al., 2020, Otani et al., 2011), circadian disruption (Fadzlina et al, 2014) abnormal glutamate metabolism (Ookonia and Pirola, 2016) and excess glucocorticoid secretion (Oraitis et al., 2017). A role for nicotinamide-N-methyltransferase (NNMT) has been suggested in the pathogenesis of MetS, due to the observed accumulation of plasma homocysteine (Giuliante, 2015; Lim et al., 2014) proposed that excessive consumption of fructose in diet can precipitate the (Parekh et al., 2014 and Festi et al. 2014) have assigned a role for the gut microbiota in the pathogenesis of MetS. Elsewhere other causes and risk factors for MetS have been listed and include age-risk being greater with increasing age, female gender, vitamin deficiency, sedentary lifestyle, and family history.

Definitions of metabolic syndrome

Just as there are multiple causes of the MetS, there are several definitions of the condition and none has received universal acceptance to date (Table 1) (Shahaz and Mohammed, 2018).

The variation in definition is due to the emphasis placed on the components of the cluster of risk factors which encompasses atherogenic dyslipidaemia, elevated blood pro-inflammatory state (NCEP, 2002; Grundy et al., 2005a; Grundy et al., 2005b). The result was confusion with the epidemiologic studies as different definitions lead to possible missed diagnosis and variability in the reported prevalence of the syndrome. More risk factors besides those traditionally used to define MetS continue to be identified (Alberti et al., 2005; Kassi et al., 2011).

The syndrome has been defined by organizations and expert bodies including National Cholesterol Education Programme/Adult Treatment Panel 111 (NCEP-ATP111) (Grundy et al., 2005a; Grundy et al., 2004), American Association of Clinical Endocrinologists (AACE) (Alberti et al., 2005), the World Health Organization (WHO, 2000), International Diabetes Federation (IDF) (Alberti et al., 2005), European Group for the Study of Insulin Resistance, EGIR) (Balkau and Charles, 1999) and the National Heart, Lung and Blood Institute, (NHLBI) (Grundy et al., 2005b). The NCEP-ATP111 (Grundy et al., 2005a) IDF (Alberti et al, 2005) definitions are the most commonly used for the diagnosis of MetS. NCEP-ATP111 definition included abdominal obesity measured as waist circumference ≥102 cm for men and ≥88 cm for women; impaired fasting glucose ≥5.6 mmol/l; high fasting triglyceride ≥1.7 mmol/l; low high density lipoprotein cholesterol (HDL-C) ≤1.0 mmol/l for men and ≤1.3 mmol/l for women; raised blood pressure ≥ 30/85 mmHg. The ATP 111 criteria (Grundy et al., 2005a) reflect their view that insulin resistance (IR) is at the root of the MetS and is diagnosed if any three or more of the factors are present. The WHO (2000) developed a definition of the metabolic syndrome that required the presence of type 2 diabetes or impaired glucose tolerance (as either impaired fasting glucose (5.6-6.9 mmol/l) or impaired glucose tolerance (7.8-11.1 mmol/l) 2 h after 75 g of glucose) or insulin resistance as well as at least two of the following: hypertension (≥140/90 mmHg or antihypertensive medication and HDLC <0.88 mmol/l; <0.98 mmol/l for men and women, respectively; obesity (BMI >30 kg/m^2 and/or waist-hip ratio >0.9 for men and >0.85 for women); raised triglycerides (≥1.7 mmol/l) and microalbuminuria. The EGIR definition required insulin resistance (plasma insulin >75th percentile) plus two or more of the following: central obesity WC≥94 cm [M], ≥80 cm [F] dyslipidaemia based on high triglyceride or low HDLC TG≥2.0 mmol/l or HDLC<0.97 mmol/l; hyperglycaemia excluding diabetes and blood pressure more than 140/90 mmHg, or treatment for hypertension, blood pressure over 130/85 mmHg; fasting triglycerides (TG) over 1.7 mmol/l and fasting HDLC. The National Heart, Lung, and Blood Institute (NHLBI) (Grundy et al., 2005b), in collaboration with the American Heart Association (AHA) (Grundy et al., 2005a) convened a conference to examine scientific issues related to definition of the metabolic syndrome from several perspectives: (1) major clinical outcomes, (2) metabolic components, (3) pathogenesis, (4) clinical criteria for diagnosis, (5) risk for clinical outcomes, and (6) therapeutic interventions, (Rundy et al., 2004). The major

Table 1. The criteria for the diagnosis of MetS as defined by different organizations/bodies (Ogbu, 2009).

Factor	Range	Organization/Body
Disglycaemia	Blood glucose ≥5.6 mmol/l	ALL
Hypertriglyceridaemia	Triglycerides ≥1.7 mmol/l	ALL
Low HDLC	Men: ≤ 1.0 mmol/l for men; ≤ 1.3 mmol/l for women	NCEP, WHO, EGIR, IDF
Excess WC	Waist circumference >102 cm for men; >88 cm for women	NCEP, EGIR, IDF
Excess WHR	Waist-hip ratio > 0.9 for men; > 0.85 for women	WHO
Raised SBP	Blood pressure > 140 mmHg	ALL
Raised DBP	Blood pressure > 90 mmHg	ALL
Obesity/Overweight	BMI ≥ 25 kg/m^2	WHO, AACE
Insulin resistance	>75^{th} percentile	WHO, EGIR

Source: Author, 2022.

factors used in the definitions of MetS are raised fasting plasma glucose, hypertriglyceridaemia, low high density lipoprotein cholesterol, increased waist circumference and raised blood pressure-either systolic or diastolic. The definitions of MetS did not differentiate the causes from its manifestations. This is as a result of the complexity of the syndrome. Some of the listed risk factors can cause the MetS or be the consequence of MetS. For example, disorders of lipid metabolism can give rise to increased levels of free fatty acids in the circulation which can also cause insulin resistance. Not all individuals with raised plasma glucose above5.6 mmol/l have MetS. However, continued rise in plasma glucose can increase the body need for insulin and precipitate insulin resistance when measured as level of circulating insulin. The usefulness of a factor may depend on whether it is the cause or effect of the syndrome. If it is a cause, it may be there early enough to serve as screening factor but as effect, its appearance may not be quite predictable. The diagnosis of MetS is commonly based on the assessment of factors of impaired glucose tolerance, dyslipidaemia, obesity, and hypertension as defined by NCEP/ATP III (NCEP, 2002) criteria.

Impaired glucose tolerance

This is assessed as either type 2 diabetes (T2D) or prediabetes. Not all individuals with the metabolic syndrome have diabetes by definition. However, in a previous study, hyperglycaemia was one of the triad most prevalent among apparently healthy subjects with the MetS. The others were low HDLC and hypertension (Ogbu, 2009). The blood glucose values are usually higher than those of individuals without the metabolic syndrome. An upper blood glucose limit of 5.5 mmol/l is recommended by the ATP 111. Most individuals with the metabolic syndrome continue to secrete large amounts of insulin and do not get the T2D. Such individuals are still at increased risk of coronary heart disease. When diabetes is not yet present, risk for progression to type 2 diabetes averages about 5-fold increase compared with those without the syndrome (Laaksonen et al., 2002; Klein et al., 2002; Lorenzo et al., 2003). Those with diabetes can further acquire a host of complications including renal failure, diabetic cardiomyopathy and various neuropathies. Disorders of glucose metabolism in MetS can either be prediabetes or type 2 diabetes. It is as a result of insulin resistance which is a constant finding in truncal/visceral obesity and other conditions such as polycystic ovarian syndrome (PCOS) (Dunaif et al., 1995). Whenever there is insulin resistance, there is likelihood of dysglycaemia and including both of them in diagnosis of MetS may be unnecessary. All definitions include raised fasting plasma glucose but not with the same cutoff point; ATP III and IDF have ≥5.6 mmol/l, WHO, 5.6 - 6.9 mmol/l, and AACE, 6.1 - 7.0 mmol/l. The WHO (2000) and Balkau and Charles, (1999) require plasma glucose above 5.6 mmol/l as evidence of insulin resistance but the cutoff point for the AACE is 6.1 mmol/l. Definitions that include 2 h post prandial plasma glucose may not be comparable with those using FPG because of the dynamics of insulin release after dietary stimulation *in vivo*. This may differ in health and in sickness. In ill health, presence of hyperglycaemia does not define the incidence of MetS. In a study of the incidence of MetS among diabetes (174), hypertension (136) and renal failure (84) subjects on drug treatment, raised plasma glucose levels (≥5.6 mmol/l) was detected in 131 (75%), 37 (27%) and 25 (30%) subjects, respectively while 125 (95%), 24 (65%) and 19 (76%), respectively had the MetS. Out of 9 apparently healthy subjects with hyperglycaemia, 7 (78%) had the MetS (Ogbu et al., 2013a; Ogbu, 2009). Raised plasma glucose is a sensitive feature of the MetS and may be used to screen for the syndrome even in apparently healthy subjects. However, there is the need for agreement on the cutoff point.

Hypertriglyceridaemia

Triglycerides (≥1.7 mmol/l) are included by all the

definitions as risk factor for MetS. The combination of high triglyceride and low high density lipoprotein is said to be the hallmark of the MetS and risk factor for ischaemic heart disease (Wilson and Grundy, 2003). With hyperinsulinaemia, hepatic output of triglyceride-rich very low density lipoprotein (VLDL) increases. Cholesterol ester transfer protein (CETP) transfers cholesterol from high density lipoprotein (HDL) in exchange for triglycerides. As a result, the concentration of HDL-C falls while that of triglycerides increases. It is usually raised in renal failure, more in males than females (Ogbu, 2009). In renal failure, there is loss of proteins especially low molecular weight ones. The body responds by increasing the production of higher molecular weight proteins that include mainly lipoproteins, very low density and low density lipoproteins that are rich in TGs. In diabetes, hypertension and renal failure subjects on drug treatment hypertriglyceridaemia is not a constant finding. In a study (Ogbu, 2009), 69, 49, 57, and 54% of DM, HTN, RF and AHS subjects, respectively had hypertriglyceridaemia. Out of those with hypertriglyceridaemia, 82, 73, 54, and 43% had MetS. Among, apparently healthy individuals, plasma levels of TG vary directly with the waist circumference. Measurement of WC, therefore, may reflect the TG levels. About 43% of apparently healthy individuals with the MetS will have hypertiglycridaemia (Ogbu, 2009). This is too low for epidemiological studies. Besides, EGIR defines a cut off of 2.0 mmol/l while others have 1.7 mmol/l and this lies within the reference range. It has been noted that the absence of elevated TG in people of African descent does not mean the absence of risk for CVD and T2D (Yu et al., 2012). In view of the different cutoff values, lack of specificity, the TG Paradox of Yu et al. (2012) and the fact that a measure of central obesity can replace measurement of serum TG, it may not be necessary to include serum TG in the diagnosis of MetS in the study population.

Low HDLC

There does not seem to be an agreement on HDLC cutoff values for male and female subjects; WHO <0.88 and 0.98; IDF and ATP III ≤1.0 and ≤1.3; AACE 1.0 and 1.3 mmol/l, respectively. In a previous study HDLC was one of the triad most prevalent among apparently healthy, diabetes, hypertension and renal failure subjects with the MetS. The others were hyperglycaemia and hypertension (Innocent et al., 2022). HDLC values are affected by environmental and perhaps dietary factors. For instance, low HDLC was the most prevalent risk factor among rural but not urban women in a study by Ogbu et al. (2013a). There is low prevalence of low HDLC in the study population and that gives it a high specificity.

Obesity

Obesity is epidemic worldwide affecting up to one third of the population of many industrialized countries of the world (James et al., 2001; Hedley et al., 2004). It is estimated that more than one billion adults worldwide are overweight and more than 300 million worldwide are obese (Misra and Vikram, 2004). The prevalence of overweight and obesity has increased dramatically both in developed and developing countries of the world in the last few dacades (Misra and Vikram, 2004; Krauss et al., 1998) Obesity is a strong and independent risk factor for type 2 diabetes mellitus, coronary heart disease (CHD), stroke, some types of cancer, hypertension, dyslipidaemia, gallbladder disease, sleep apnoea, osteoarthritis (Musta et al., 1996; Fontaine et al., 1996) as well as psychosocial consequences, such as a limitation of capacity for physical activity (Department of Agriculture, 1980; Innocent et al., 2022). Obesity gives rise to some of the criteria for the diagnosis of the MetS such as T2D, hypertension, and dyslipid aemia.

Guidelines for healthy weight are traditionally set based on the range of weights that correspond to the lowest mortality. However, there is the problem of reverse causation; people frequently lose weight as a result of illness that may ultimately be fatal giving the impression of higher mortality among those with lower weight. Conditions that lead to weight loss could remain undiagnosed for years; examples are alcoholism, cancer, and depression. Secondly, confounding factors may distort the association between body weight and mortality, e.g. smoking (smokers tend to weigh less and have higher mortality than non-smokers), alcoholism, composition of diet, and physical activity. Healthy weight has been given as BMI range between 21 and 25 according to the Dietary Guidelines for Americans published in 1980 (Department of Agriculture,1980) and this is consistent with that recommended by a Steering Committee of American Institute of Nutrition and an Expert Committee of the WHO (1995).

Obesity in the diagnosis of MetS is assessed as either body mass index (BMI), waist circumference, (WC) or waist-hip ratio (WHR) and it is a measure of total adipose tissue. Other possible methods include dual-energy x-ray absorptiometry, skin fold thickness and bio-impedance. WC is included in the criteria by NCEP, EGIR, and IDF. Only WHO includes WHR while WHO and AACE included BMI.

Hence, WC is the most popular measure of body weight in the diagnosis of MetS. The measurement of body circumference is important because of excess visceral fat as a risk factor for chronic disease. Waist circumference and ratio of waist to hip circumference have been used for this purpose (Schreiner et al., 1996). They correlate with measures of risk factor for CHD such as hypertension and blood lipids (James, 2001; Han et al., 1995). For WC, upper limits of 102 and 89 cm have been suggested for men and women, respectively. At identical BMI, women will, on average, have more body fat than men (Gallagher et al., 1996). BMI calculation has body weight as a factor.

The absence of weight gain particularly among adult of more than 50 years of age does not indicate that fat has not increased. Muscle mass is to a varying degree replaced by fat, much of it within the abdomen leading to increasing waist circumference. BMI does not differentiate between lean and fat mass and may not be very reliable in older adults in whom differential loss of lean mass contribute increasingly to variations in weight. Since the point of assessment is body fat, BMI may not be a sensitive factor.

Raised blood pressure

Hypertension is a strong risk factor for ischaemic heart disease (IHD) (MacMahon et al., 1990). It results from increased peripheral resistance which maintains elevated arterial blood pressure. The increase in peripheral resistance results in part, from abnormal constrictor and dilator responses and vascular re-modeling. Development of hypertension in individuals with the MetS, might relate to the regulation of nitric oxide (NO), which has strong vasodilatory functions (Yang and Zhang, 2004).

Hyperinsulinaemia can cause hypertension by one or a combination of four mechanisms; (1) sodium ion retention; (2) sympathetic nervous system over-activity; (3) disturbed membrane ion transport; (4) proliferation of vascular smooth muscle cells. Physiological manoeuvers such as physical exercise that improves insulin resistance also lowers blood pressure (Virkamaki et al., 1996; De-Fronzo and Ferrranni, 1991). All definitions contain the factor of raised blood pressure, 130/85 mmHg (WHO 140/90 mmHg).

Insulin resistance

The WHO criteria emphasize insulin resistance (IR) as factor in the diagnosis of MetS (Alberti et al., 2005). This is measured as increase in fasting (≥5.6 – 6.9 mmol/l) and 2-h post prandial (7.8 - 11.1 mmol/l) plasma glucose. IR underscores the inability of insulin to promote normal homeostasis of glucose. It is a prevalent medical condition that accompanies prediabetes, type 2 diabetes, obesity, hypertension, metabolic syndrome and polycystic ovarian disease (WHO, 2000; Wang et al., 2004). It may result from impaired insulin signaling due to mutation or posttranslational modification of the insulin receptor itself or any of its downstream effector molecules or defect in insulin binding to its receptor (Dunaif et al., 1995; Balkau and Charles, 1999). Insulin functions not only as a peripheral regulator of nutrient storage and release of circulating substrates but as a key efferent signal to the central nervous system for the control of energy balance. Reduced central nervous system and peripheral insulin signaling from either defective secretion or action contributes to the pathogenesis of diabetes and obesity (Laaksonen et al., 2002). The ventral hypothalamus is the key brain area in energy homeostasis. The various inputs the brain uses to adjust food intake can be subdivided into two groups; those that communicate information pertaining to body energy store and those that are generated acutely in response to nutrient ingestion (Belson, 2004). Of the former group, insulin and leptin are the best studied and understood and both appear to be required by the central nervous system for the control of food intake, body weight and metabolic homeostasis (Le-Roith and Zick, 2001). Leptin is an adipocytokine which concentration and that of insulin correlate with body fat mass and they exert relatively long-lived inhibitory effects on food intake via action on a common set of hypothalamic neurons (Porte et al., 2002). The coexistence of insulin resistance and hypertension can be viewed as cause-effect or non-causal association.

Insulin resistance and obesity

Whether IR is the cause or consequence of obesity remains a matter of conjecture, although, it is likely that both are true. Adipocytes are very sensitive to insulin action. Adipocyte biology can be regulated by insulin in a number of mechanisms that include facilitating differentiation of preadepocytes to adepocytes, stimulating glucose transport and lipid metabolism in mature ones. Products of adipocyte metabolism can also cause IR. The antilipolytic effect of insulin requires much lower insulin concentration than stimulation of glucose transport. Hence, glucose transport may be impaired in IR while its antilipolytic action is preserved leading to increase in adipose stores (Porte et al., 2005). Obesity, however, has not one aetiology, one pathogenesis, and certainly not one treatment. The belief that obesity results simply from over-eating or from a sedentary lifestyle has influenced thinking for a long time. However, it is becoming increasingly apparent that the body has a highly complex and sophisticated system of regulating fat storage and energy balance (Leibel et al., 1995). IR seems to link different components of the MetS together (Parekh et al., 2014, 2014) while IR and T2D have been linked to obesity (Ahjoub and Massrou-Roudsari, 2012).

The ventral hypothalamus is the key brain area in energy homeostasis. Dual signal from the brain regulate food intake and storage; one that is acute is for intake and the other, chronic, is for storage (Schwartz, 2000).

CONCLUSION

The major factors for the diagnosis of the MetS according to ATP111 criteria are IR measured as elevated fasting plasma glucose that falls within the upper limit of the reference range and lower limit of the diabetes range, obesity measured as increased WC and dislipidaemia of

the high triglyceride, low high density lipoprotein cholesterol type and hypertension. From the discussions, it has been established the both IR and obesity can give rise to all these factors and to each other. Therefore, if efforts are made to streamline the diagnosis of IR and obesity, there may not be need for the other varying specifications and criteria of universal application could emerge.

ABBREVIATIONS

NCEP, National Cholesterol Education Programme; **EGIR,** European Group for the Study of Insulin Resistance; **IDF,** International Diabetes Federation; **AACE,** American Association of Clinical Endocrinologists; **MetS,** metabolic syndrome; **T2D,** type 2 diabetes; **CHD,** coronary heart Disease; **NNMT,** nicotinamide-N-methyltransferase; **NCEP/ATP 111,** National Cholesterol Education Programme/Adult Treatment Panel 111; **NHLBI,** National Heart, Lung and Blood Institute; **IR,** insulin resistance; **AHA,** American Heart Association; **HDLC,** high density lipoprotein cholesterol; **WHR,** waist hip ratio; **SBP,** systolic blood pressure; **DBP,** diastolic blood pressure; **BMI,** body mass index; **IHD,** ischaemic heart disease; **WC,** waist circumference; **CEPT,** cholesterol ester transfer protein; **CVD,** cardiovascular disease; **TG,** triglyceride.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Afar U, Khaliq S, Ahmad HU, Manzoor S,and Lone KP (2018). Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links. Hormones 17(3):299-313.

Ahjoub S, Massrou-Roudsari J (2012) Role of oxidative stress in the pathogenesis of metabolic syndrome. Caspian internal medicine 3(1):386-396.

Alberti KGMM, Zimmet P, Shaw J (2005). International Diabetic Federation, (IDF), Epidemiology Task Force Consensus Group. The Metabolic Syndrome – a new worldwide definition Lancet 366(9491):1059-1062.

Balkau B, Charles MA (1999). Comments on the provisional report from the WHO Consultation. European Group for the Study of Insulin Resistance (EGIR). Diabetic Medicine 16:442-443. http://dx.doi.org/10.1046/j.1464-5491.1999.00059.x

Belson Kennedy D (2004). The obesity epidemic. Science 304:1413-1415

Chlup R, Bartek J, Reznickova M, Zapletalová J, Doubravová, B, Chlupová L, Simánek V (2004). Determination of the glycaemic index of selected foods (white bread and cereal bars) in healthy persons. Biomed Papers 148(1):17-25.

De-Fronzo RA, Ferrranni E (1991). Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. *Diabetes Care* 14 (3):173-174.

Department of Agriculture, Department of Health and Human Services, (1980). Nutrition and your health: Home and Garden Bulletin No 232. Washington DC: Government Printing Office.

Dunaif A, Xia J, Book CB, Schenker E, Tang Z (1995). Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. The Journal of clinical investigation 96(2):801-810.

Fadzlina AA, Harun F, Nurul Haniza MY, Al Sadat N, Murray L, Cantwell MM, Su TT, Majid HA, Jalaludin MY (2014). Metabolic syndrome among 13 year old adolescents: prevalence and risk factors. BMC Public Health 14(3):1-8

Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A (2014). Gut microbiota and metabolic syndrome. World Journal Gastroenterol 20(43):16079

Fontaine KR, Cheskin LJ, Barofsky. I (1996). Health-related quality of life in obese persons seeking treatment. Journal Family Practice 43(1):265-270.

Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB (1996). How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups. American Journal of Epidemiology 143(1):228-239.

Giuliante, R, Sartini D, Bacchetti T, Rocchetti R, Klöting I, Polidori C, Emanuelli M (2015). Potential involvement of nicotinamide N-methyltransferase in the pathogenesis of metabolic syndrome. Metabolic Syndrome and Related Disorders 13(4):165-170.

Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C (2004). Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 109(3):433-438.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Costa F (2005a). Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 112(17):2735-2752.

Grundy SM, Cleeman JI, Daurels SR (2005b). Diagnosis and management of the metabolic syndrome; a statement for healthcare professionals: an American Heart Association/National Heart, Lung, and Blood Institute scientific Statement. Circulation 112(21):2735-2752.

Han TS, van Leer EM, Seidell JC, Lean MEJ (1995). Waist circumference action level in the identification of cardiovascular risk factors: prevalence study in a random sample. British Medical Journal 311(7017):1401-1405.

Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM (2004). Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. Jama 291(23):2847-2850.

Innocent O, Chinemerem O, Emmanuel N, Samuel U, Elizabeth A, Clementina E, Ogbu O (2022). Frequency of diagnostic combination of risk factors of metabolic syndrome associated with diabetes, hypertension, chronic kidney disease and apparent health. Journal of Medical Laboratory and Diagnosis 12(1):6-10.

James PT, Leach R, Kalamara E, Shayeghi M (2001). The worldwide obesity epidemic. Obesity Research 9(Suppl 4):228S-233S.

Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM (1976). The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. New England Journal Medicine 294(13):739-745.

Kahn CR, Wang G, Lee KY (2019). Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. The Journal of clinical investigation 129(10):3990-4000. Doi: 10.1172/JCI129187

Kassi PP, Kaltsas G, Chrousos G (2011). Metabolic syndrome: definitions and controversies. BMC medicine 9:1-13.

Klein BE, Klein R, Lee KE (2002). Components of the metabolic syndrome and risk of cardiovascular disease and diabetes beaver dam. Diabetes Care 25(10):1790-1794.

Krauss RM, Winston M, Fletcher RN, Grundy S.M (1998). Obesity: impact of cardiovascular disease. Circulation 98(15):1472-1476.

Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA (2002). Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. American Journal of Epidemiology 156(11):1070-1077.

Leibel RL, Rosenbaum M, Hirsch J (1995). Changes in energy expenditure resulting from altered body weight. New England Journal of Medicine 323(10):621-628.

Le-Roith DA, Zick Y (2001). Recent advances in our understanding of insulin action and insulin resistance. Diabetes Care 24(3):588-597.
Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH (2010). The role of fructose in the pathology of non-alcoholic fatty liver disease and metabolic syndrome. Nature reviews Gastroenterology & hepatology 7(5):251-264.
Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM (2003). The metabolic syndrome as predictor of type 2 diabetes: The San Antonio Heart study. Diabetes Care 26(11):3153-3159.
MacMahon S, Peto R, Cutler J, Collins R, Solie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler, J, (1990). Blood pressure, stroke and coronary heart disease, 1: prolonged differences in blood pressure perspective observational studies corrected for the regression dilution bias. Lancet 335(8692):765-774.
Misra A, Vikram NK (2004). Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. Nutrition 20(5):482-491.
Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH (1999). The disease burden associated with overweight and obesity. JAMA 282(16):1523-1529.
National Cholesterol Education Programme (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
Ogbu ISI (2009). Incidence of metabolic syndrome among hospital-based patients in the University of Nigeria Teaching Hospital and apparently healthy people in Enugu metropolis. A PhD thesis, University of Calabar, Nigeria.
Ogbu ISI, Udoh AE, Oforegbu EN (2013a). The prevalence of the metabolic syndrome among type 2 diabetes patients in Enugu, Southeastern Nigera. World Journal of Medical Sciences Recourses 1:6-11.
Ookonia S, Pirola CJ (2016). Non alcoholic fatty liver disease and metabolic syndrome: Shared genetic basis of pathogenesis. Hepatology 64(5):1417-1420.
Oraitis AG, Block T, Nguyen D, Belanoff JK (2017). The role of glucocorticoid receptors in metabolic syndrome and psychiatric illness. The Journal of steroid biochemistry and molecular biology. 165:114-120.
Otani H (2011). Oxidative stress as pathogenesis of cardiovascular risk associated with metabolic syndrome. Antioxidants & redox signaling, 15(7):1911-1926.
Parekh PJ, Arusi E, Vinik AI, Johnson DA (2014). The role and influence of gut microbiota in pathogenesis and management of obesity and metabolic syndrome. Frontiers in endocrinology 5:47 doi 10:3389/fendo2014.00047
Porte D Jr, Baskin DG, Schwartz MW (2002). Insulin signaling in the central nervous system. Diabetes 54(5):1264-1276.
Porte D Jr, Baskin DG, Schwartz MW (2005). Leptin and insulin action in the central nervous system. Nutrition Review 60:520-529.
Roach P, Zick Y, Formisano P, Accili D, Taylor SI, Gorden P (1994). A novel human IR gene mutation uniquely inhibits insulin binding without impairing posttranslational processing. Diabetes 43:1096-1102.
Schreiner PJ, Terry JG, Evans GW, Hinson WH, Crouse III JR, Heiss G (1996). Sex-specific associations of magnetic resonance imaging-derived intra-abdominal and subcutaneous fat areas with conventional anthropometric indices: The Atherosclerosis Risk in Communities Study. American journal of epidemiology 144(4):335-345.
Schwartz MW (2000). Central nervous system control of food intake. Nature 404:661-671.
Shahaz T, Mohammed A (2018). The role of lipids in the pathogenesis of metabolic syndrome in adolescents. Exptal and Clin Endocrinol Diabetes 126(10):14-22.
Smith M, Honce R, Schultz-Cherry S (2020). Metabolic syndrome and viral pathogenesis: lessons from influenza and coronaviruses. Journal of virology 94(18):e00665-20.
Titov VN (2014). Leptin and adeponectin in pathogenesis of metabolic syndrome. Klinicheskaia Meditsina 92(4):20-29.
Virkamaki A, Ueki K, Kahn CR (1996). Protein-protein interaction in insulin signaling and the molecular mechanism of insulin resistance. Journal of Clinical Investigations 103:931-943.
Wang CC, Goalstone ML, Draznin B (2004) Molecular mechanisms of insulin resistance that impact on cardiovascular biology. Diabetes 53(11):2735-2740.
Wang HH, Lee DK, Liu M, Portincasa P, Wang DQ (2020). Novel insight into the pathogenesis and management of the metabolic syndrome. Pediatric Gastroenterology, Hepatology and Nutrition 23(3):189-230
Wilson PW, Grundy SM (2003). The metabolic syndrome: a practical guide to origins and treatment: Part II. Circulation 108(13):1537-1540.
World Health Organization (2000). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894; i – ix, 1 -25.
World Health Organization (2000). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894; i – ix, 1 -253.
World Health Organization (WHO) (1995). Physical status: the use and interpretation of anthropometry; report of a WHO Expert Committee. WHO Technical Report Series 854:1-452.
Yang S, Zhang L (2004). Glucocorticoids and vascular reactivity. Current Opinions in Vascular Pharmacology *2*(1):1-2.
Yu SS K, Castillo DC, Courville AB, Summer AE (2012). The triglyceride Paradox in people of African descent. Metabolic syndrome and related disorders 10(2):77-82.