ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Metabolic Syndrome: Evolution, Etiopathogenesis and Recent Trends in Its Management.

Kunal Sharma[1]*, Rasmirekha Behera[2], Divya Agrawal[3], Sanjay Kumar[4]

[*1]Resident and Tutor, Dept of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India.
[2]Assistant Professor, Dept. of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[3]Assistant Professor , Dept. of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[4]Professor, Dept. of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India.

ABSTRACT

Metabolic syndrome is a very complex disorder defined by a bundle of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases and diabetes mellitus type 2, Dyslipidemia, abdominal obesity, diabetes mellitus and high blood pressure are together defined as risk factors for cardiovascular disease triggered by metabolic syndrome. The metabolic syndromes have a relationship with the variations in genetic susceptibility, nutritional regimen, physical exercise, chronological age and gender which are directly associated with the incidence of metabolic syndrome and its side effects. . Now a days, many different definitions of Metabolic Syndrome are available, among them the latest and most accepted definitions are WHO, ATP III and International Diabetes Federation (IDF). The clinicians should seriously consider risk screening program for all people regardless of age for abnormalities in glucose level. Early treatment in people with disturbed blood glucose level constitutes a strategy of preventing type 2 diabetes mellitus and further metabolic syndrome.

Keywords: metabolic syndrome, diabetes mellitus, obesity

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Metabolic syndrome is a group of clinical findings which leads to major chronic disease of the morden era. Among the various conditions the glucose intolerence, hypertension, increased very-low-density lipoproteins (VLDL), triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C), with insulin resistance are considered as the basic underlying pathophysiologic problem[1,2,3]. Obstructive Sleep Apnoea and Metabolic Syndrome are considered to act synergistically to aggravate cardiovascular risk and When metabolic syndrome is associated with obsturctive sleep apnoea then it termed as syndrome- Z [4,5]. This syndrome is directly increase the risk of coronary heart disease (CHD), other forms of cardiovascular atherosclerotic diseases (CVD), and diabetes mellitus type 2 (DMT2). The abnormalities like chronic pro-inflammatory state, non- alcoholic liver disease and prothrombotic conditions are added recently to the metabolic syndrome entity. The metabolic syndrome not only affects adults and older people but it is also affecting in children and teen agers with very high incidence and the future implications to the global health burden it may confer[6-8].

EVOLUTION OF DEFINITION:

About two and half century back, an Italian physician and anatomist, Morgagni identified that there has been certain relationship between visceral obesity, hypertension, atherosclerosis, hyperuricemia and obsturctive sleep apnoea[9].

Nicolae Paulescu has reported the association between diabetes and obesity in 1920. He said “most frequently, the obese people become glycosuric, as if the two affections (obesity and fat diabetes) represent two consequent phases of the same pathological process” [10].

The founder of modern endocrinology, Maranon of Spain in 1927, described that the arterial hypertension and obesity is pre-diabetic condition. Maranon also believed that food is essential for preventing and treating these metabolic disturbances .In 1947, a French physician Vague was the first person to identify android obesity (obesity of the upper part of the body) as the condition being most commonly associated with diabetes mellitus and cardiovascular diseases [9].

In the 1960s, the term “plurimetabolical syndrome” was given to the condition in which frequent simultaneous presence of obesity, dyslipidemia, diabetes mellitus and systemic hypertension[11]. In the 7th decades of the last century, many researchers have supported the idea of the existence of a close relationship among the factors that constitute the metabolic syndrome at present, correlating them with the cardiovascular diseases and the atherosclerosis is considered by a complex inequilibrium of the metabolism, vaso-motility, coagulation and hydroelectrolytic and mineral equilibrium[12-14].

In 1975, Hermann Haller introduced the term, “Metabolic Syndrome” in his scientific literature[15]. Two years later in 1977, Haller used the term “metabolic syndrome” for the association of obesity, diabetes mellitus, dyslipidemia, hyperuricemia and fatty liver while describing the relative effects of risk factors on atherosclerosis[16].

In late1980s, the glucose and insulin metabolism disorder, obesity, dyslipidemia, and hypertension was grouped together and coined as mysterious name, 'Syndrome X' by Reaven G., an endocrinologist from Stanford University. He proceeded forward with explaining the relationship between diabetes, obesity, dyslipidemia and systemic hypertension by their pathogenic involvement with the peripheral insulin-resistance with compensatory hyper- insulinemia[3]. In fact, the metabolic syndrome represents complex disturbances of the glucose storing metabolism in close relationship with altered insulin secretion, which is influenced by the sensitivity / resistance to insulin[17]. Later many studies showed that the spectrum of metabolic Disturbances was bigger. Ferranini and colleagues carried out further studies and confirmed that the grouping was done in the basis of insulin resistance, and after few years they coined a new term 'insulin resistance syndrome[9]. In the year of 1992, Zimmet and Serjentson termed "plus X syndrome" when there is associated hyperuricaemia, sedentary life style with old age[18].

The metabolic syndrome was first defined by WHO (World Health Organization) in the year 1998 by the work group of Diabetes. Then subsequent revision was taken place and in 1999 a new definition came along with diagnostic criteria. The Metabolic syndrome is defined by the presence of type -2 Diabetes mellitus or prediabetic condition[19] or insulin resistance associated with minimum of 2 other factors like, hypertension, dyslipidemia, obesity and microalbumineria [20].

- Waist / hip ratio — >90cm in males, > 85cm in females.
- Serum triglycerides level — ≥150 mg/dl.
- HDL cholesterol level — <35 mg/dl in males, <39 mg/dl in females.
- Microalbumineria — >20 µg/min.
- Blood pressure — ≥140/90 mmHg.

In the next year 1999, EGIR (European Group for the Study of Insulin resistance) had given opinion for the slight changes in the definition of WHO with emphasis on insulin-resistance. The insulin resistance was considered to be a major cause of metabolic syndrome[21] and also given more importance to the abdominal obesity than WHO, but they excluded the person with diabetes mellitus type 2.EGIR defined metabolic syndrome as[22]Insulin-resistance or hyperinsulinemia à jeun (on empty stomach) >25% along with 2 other parameters like :

- Blood glucose à jeun (on empty stomach) (excluding diabetes) — ≥ 6.1 mmol/ l
- Blood presure (or patient on the treatment for systemic hypertension) — ≥ 140/90 mmHg
- Serum triglyceride levels — ≥ 2 mmol/l
- HDL cholesterol levels (or patient on treatment for dyslipidemia) — < 1 mmol/l
- Waist circumference — ≥ 94 cm in males and ≥80 cm in females.

ISSN: 0975-8585

In 2001 NCEP-ATP III (the USA Cholesterol Education Panel, Adult Treatment Panel III) introduced new and simple clinical criteria for the diagnosis of Metabolic Syndrome. They removed insulin- resistance condition from its criteria for diagnosis[23,24]. ATP III considered a person having metabolic syndrome when fulfilling at least three of the mentioned criteria:

- Waist circumference — ≥102 cm in males and ≥ 88 cm in females
- Serum triglyceride level (or patient on drug treatment) — ≥150 mg/dl
- HDL cholesterol level (or patient on drug treatment) — <40 mg/dl in males and <50 mg/dl in females
- Systemic Blood pressure (or patient on drug treatment) — ≥130 / 85 mmHg
- Blood glucose levels (or patient on drug treatment) — ≥100 mg/dl

Revised NCEP-ATP III criteria were given by AACE (American College of Endocrinology) in 2003, in which prediabetic condition was consider again with few more additions in diagnostic parameters [25]. The major criteria were impaired glucose tolerance, elevated triglycerides, reduced HDL-C, elevated BP, and obesity along with other factors like, family history of atherosclerotic cardiovascular disease or type 2 DM, polycystic ovary syndrome, and hyperuricemia be considered while exercising clinical judgement. The components which suggested by the AACE are as follows:

1. The glucose intolerance (excluded type 2 diabetes)
    - Impaired fasting glucose level / impaired glucose tolerance
2. Abnormalities in uric acid metabolism
    - Plasma concentration of uric acid
    - Renal clearance of uric acid
3. Dyslipidemia
    - Increase in Triglycerides level
    - Decrease in HDL-C
    - High LDL particle diameter (small, dense LDL-particles)
    - Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
    - Sympathetic nervous system over - activity
    - Renal sodium retention
    - Blood pressure (~50% of patients with hypertension are insulin resistant)
5. Prothrombotic factors
    - Plasminogen activator inhibitor-1
    - Fibrinogen
6. Markers of inflammation

- C-reactive protein, white blood cell count, etc.

7. Endothelial dysfunction
    - Mononuclear cell adhesion
    - Plasma concentration of cellular adhesion molecules
    - Plasma concentration of asymmetric dimethylarginine
    - Endothelial-dependent vasodilatation

In 2005 IDF (the International Diabetes Federation) came into the picture and modify the ATP III definition, formulated the new criteria for diagnosis and believed central obesity (waist circumference) is the main patholgical culprit for the development of metabolic syndrome . The panel also considered some 'optional parameters' like C-Reactive protein as for pro-inflammatory condition, high fibrogen for a marker for pro-thrombotic status[9,26].

In 2009, the International Diabetes Federation (IDF) and the American Heart Association/ National Heart, Lung and Blood Institute (AHA/NHLBI) supported that waist measurement depending upon race and gender would be taken as a useful preliminary screening tool instead of central obesity. Three out of five findings would be considered for the diagnosis of metabolic syndrome[27,28].

1. Increase waist circumference (depending upon race and gender)

For Europeans	≥94 cm for males and ≥80 cm for females.
For non- Europeans	≥102 cm for males and ≥88 cm for females.
For south asians, chinese and japanese	≥90cm for males and ≥80 cm for females.

2. high triglyceride levels ≥150mg/dl

(or drug treatment for triglyceridemia)

3. decreased HDL-cholesterol levels < 40 mg/dl in males and or

(Drug treatment for dyslipidemia) < 50 mg/dl in females

4. high systemic blood pressure ≥130 /85mmHg

(Antihypertensive drug treatment)

5. high level of fasting glucose ≥100 mg/dl

(Drug treatment of diabetes)

Despite of many changing definition the term "metabolic syndrome" demonstrated its capacity to survive even in a hostile scientific environment. Definitions and diagnostic criteria of the syndrome were disputed, but the name survived. Most important, the hypothetical concept rationally changed into explanatory physiological model, which represents an easy risk assessment model to identify the individuals at risk of developing CVD and diabetes. Thus, we have accepted the term "Metabolic Syndrome".

ISSN: 0975-8585

Epidemiology of the Metabolic Syndrome

The differences in the genetic background, dietary habits, lifestyle, age and sex influence the prevalence of both metabolic syndrome and its associated components[29]. Due to many definitions highlighted in various studies, it is difficult and conflicting to enumerate the changes in the temporal trends and regional variations in the prevalence of this syndrome. By the latest diagnostic guidelines the region-specific cut-points for waist circumference has come into practice to know the level of obesity, and so, for defining metabolic syndrome. After consideration the fact of the relationship between obesity and glucose intolerance[30], blood pressure [31] and dyslipidemia [32] varies between ethnic groups, the identification of the metabolic syndrome become slight tricky and may mask some of the important regional differences in the prevalence rate of the syndrome.

The World Health organization predicted the prevalence rate of obesity was 4.8% in low developed countries, 17.1% in developing countries and 20% in developed countries[37]. The prevalence of metabolic syndrome increases by age may be because of prevalence of obesity, hypertension, dyslipidemia and hyperglycemia all increases with age. Among U.S. adult population, the prevalence rate of obesity (BMI ≥ 30) has increased by more than 2 folds, from 15% in the early 1970s to 34% in 2009–2010[33,34]. Similar patterns are observed in many countries and were also comparable to different age, ethnic, educational and income groups[35]. It is estimated that with the present trend of increasing prevalence of obesity, the absolute number of obese individuals could rise to a total of 1.12 billion by 2030, which will account for 20% of the world's adult population[36].

TABLE-1: GEOGRAPHICAL VARIATION OF METABOLIC SYNDROME PREVALENCE

				Prevalence (%)								
Country	**Study population year**	**Total number of subjects**	**Population group**	**Overall**	**Males**	**Female**	**Hyper TG**	**Low HDL**	**hypertension**	**Impaired glucose tolerence / hyperglycemia**	**OBESITY**	**Study**
USA	2009-2010	2034	Mexican-American (MA), non-MA white (hereinafter white), or non-MA black (hereinafter black)	22.9	----	----	24.3	30.1	24.0	19.9	56.1	**Hiram Beltrán-Sánchez et.al.[37]**
UK	1999/2000	7306	British people	10.7	7.0	3.5	12.9	5.2	13.6	1.5	22.9	**UK NCD[38]**

ISSN: 0975-8585

				Prevalence (%)								
Country	**Study population year**	**Total number of subjects**	**Population group**	**Overall**	**Males**	**Female**	**Hyper TG**	**Low HDL**	**hypertension**	**Impaired glucose tolerence / hyperglycemia**	**OBESITY**	**Study**
GERMANY	2005	2987	Population of the city Augsberg, Germany	14.8	7.6	7.2	10.6	9.4	19.1	8.4	26.3	**KORA**[39]
FINLAND	2008	3685	Finnish population	18.4	8.7	9.6	11.0	9.4	21.7	13.4	25.7	**FINRISK 2007, DILGOM**[40]
Norway	1995-1997	61199	Norwegian population	9.6	4.5	5.1	7.6	7.4	13.0	2.25	16.2	**HUNT–2**[41]
ITLAY	2002-2003	1117	Italian population	4.6	2.3	2.3	4.0	1.5	7.4	2.4	11.6	**CHRIS**[42]
Brazil	Publication year 2013	8505	Brazilian adult population	29.6			24.0	59.3	52.5	16.0	39.8	**de Carvalho Vidigal et al.**[43]
Kenya	2008	539	urban population in Kenya	34.6	29	40.2	m- 63.3, f- 30.6	m- 80.0, f – 96.3	m- 96.2, f- 89.8	m- 26.9, f – 26.9	m- 80.8, f – 97.2	**Lydia U. Kaduka et al.**[44]
Jamaica	2005-2007	839	**Jamaican young adults**	1.2	0.5	1.7	0.6	46.8	6.7	1.2	16.0	**Trevor S Ferguson et al.**[45]
Nigeria	2008	973	**Nigerians Population**	86.0	83	86	69	23	67	------	80.0	**Anthonia O Ogbera et al.**[46]
China	2000-2010	3561	**Chinese population**	21.3	16.3	30.9	17.4	71.1	40.8	53.1	25.4	**Xiang Qian Lao et al.**[47]
Russia	2000	**3705**	**Russian adults**	23.1	24.4	44.8	m- 32.2, f- 29.7	m- 32.9, f- 49.3	m- 68.5, f- 62.1	m- 12.1, f- 10.7	m- 12.1, f- 47.6	**Arkhangelsk study**[48]
Iran	2002-	**2941**	Urban	23.7	23.1	24.4	M- 43.0,	M-	M- 22.6,	M -18.1,	M-	**F.**

ISSN: 0975-8585

				Prevalence (%)								
Country	**Study population year**	**Total number of subjects**	**Population group**	**Overall**	**Males**	**Female**	**Hyper TG**	**Low HDL**	**hypertension**	**Impaired glucose tolerence / hyperglycemia**	**OBESITY**	**Study**
	2003		population of west part				f- 38.4	63.0, F- 93.3	f- 19.8	f- 19.2	10.6, F- 41.4	**Sharifi et al.**[49]
Korea	April to June 2007	**1545**	Korean workers	21.0	28.5	11.8	29.1	64.4	12.6	21.5	26.5	**DR KANG et al.**[50]
South africa	Using 1996 census	**947**	rural African (black) community of Zulu descent	23.3	10.5	25.0	M 13.8, f- 11.7	m- 29.1, f- 65.2	m- 47.1 f- 48.4	m- 13.8, f- 10.6	m- 16.4, f- 62.4	**Motala and Associates et al.**[51]
Japan	2000-2004	22,892	Japanese population	10.5	14.0	2.9	14.8	8.2	26.9	11.7	8.9	**Mitsuyoshi urashima et al.**[52]
Sri Lanka	2005-2006	4485	Sri Lankan Moors (Muslims), followed by Sinhalese and Tamils	24.3	18.4	28.3	-----	------	------	----------	---------	**Prasad Katulanda et al.**[53]
Pakistan	2011	1329	Urban Pakistan populaton	63.7			41.6	58.7	54.9	63.4	70.3	**Niloufer Sultan Ali et al.**[54]
	2011	193	young adults between 17 and 25 years of age				20.2	87.6	23.8	4.7	34.7	**Madiha Ahmad et al**[55]
INDIA	October, 2009-October, 2011	899	North Indian Adolescents aged 10- 18 years	1.5	1.90	1.30	31.0	17	4.0	9.8	3.70	**Bhat et al.**[56]

ISSN: 0975-8585

				Prevalence (%)								
Country	**Study population year**	**Total number of subjects**	**Population group**	**Overall**	**Males**	**Female**	**Hyper TG**	**Low HDL**	**hypertension**	**Impaired glucose tolerence / hyperglycemia**	**OBESITY**	**Study**
	January 2010 to June 2011	1200	rural population of Ambala district	9.2	6.45	11.64			53.63	88.8		**Pathania, *et al.*[57]**
	2010 - 2011	500	General population	25.6	29.0	23.0	33.0	36.0	28.0	29.0	29.0	**Seerat Hussain Beigh at al.[58]**
	2011	560	Population based survey of cohort in the metropolitan city of Mumbai	19.52	25.16	12.6	38.13	47.97		39.96	33.75	**Sawant et al.[59]**
	2001	1178	urban population of Berhampur city of Orissa state in Eastern India	33.5	24.9	42.3	37.7	46.9	63.1	31.2	48.9	**Prasad et al.[60]**
	2005	1077	Industrial population in Chennai	41.3			45.2	70.3	39.6	45.9	52.8	***Prabhdeep Kaur et al.[61]***

Obstructive sleep apnoea (OSA) has been also shown to be associated with metabolic syndrome and carry similar type of risk factors like hypertension[62,63] insulin resistance[64,65] and dyslipidemia [66]. The study showed the prevalence of Metabolic Syndrome in patient with OSA in United Kingdom[66] was 85 per cent compared with 37 per cent in healthy person, in Chinese population 58% compared with 21 per cent in normal individuals[67]. The another study from north India showed the prevalence of Metabolic Syndrome in a person with OSA was 77% and 40% in healthy normal people[68]. However, the data on the relationship between OSA and Metabolic Syndrome are conflicting with obesity being belived as an important confounder due to its independent association with OSA and other cardiovascular risk factors[69-71].

However, the recent evidence indicates that obesity not in every case lead to adverse metabolic effects such as impaired glucose tolerance, insulin resistance, dyslipidemia and hypertension[72], a cluster of the obesity-driven alterations also known as the metabolic syndrome[73, 74]. A subgroup of approximately 10-30% of obese individuals is metabolically healthy despite having excessive accumulation of body fat[75-80]. This phenomenon is referred to in the current literature as metabolically healthy obesity (MHO)[81]. However, to date, little is known about the factors that delay onset of or protect obese individuals from developing metabolic disturbances[82].

Pathophysiology of Metabolic Syndrome

Now the days term Metabolic Syndrome has become a hot topic for discussion in medical literature. Metabolic Syndrome is the result of complex inter-relationship between genetic and other factors like physical inactivity, ageing, a pro-inflammatory state and hormonal changes, but the role of these may depends on the ethnic group [31, 83]. Despite the progress in our understanding of the metabolic syndrome, its pathophysiology remains unclear[9]. It is necessary to understand the pathophysiology of this syndrome for all medical professionals in order to identify people at risk of development of diabetes and cardiovascular disease. Early identification of people at risk will help in early intervention for prevention[84, 85]. Although the cause of the syndrome is uncertain, strong hypotheses implicate to central obesity and insulin resistance[6,86] as the core of the pathophysiology as shown in figure-1. The other factors for inflammation and pro-inflamatory condition[87,88] such as chronic stress, and dysregulation of the hypothalamic- pituitary- adrenal(HPA) axis and autonomic nervous system (ANS), increases in cellular oxidative stress, renin-angiotensin-aldosterone system activity, and intrinsic tissue glucocorticoid actions, as well as newly discovered molecules such as micro RNAs can also be involved in its pathogenesis.

Insulin resistance

Insulin resistance occurs when cells of skeletal muscle, hepatic cells and adipose tissue decrease its sensitivity and eventually resistant to insulin action, which results into inablity to absorb glucose by these cells & remains in the blood at increased level. Excess of glucose in the blood itself trigger the insulin secretion from the beta cells of pancrease, for the need of more and more insulin (hyperinsulinaemia, a pre-diabetic condition) to be produced in an attempt to process the glucose at normal level in case if insulin resistance. The other additional factors for pre-diabetic condition include defects in the secretion of insulin and insulin receptor signaling, impaired glucose disposal, and pro- inflammatory cytokines. The association of impaired glucose tolerance and Insulin resistance is well documented by many researchers. The persistent state of hyperinsulinemia itself cause destruction of the beta cells. When beta cells are not able to produce enough insulin then a person becomes hyperglycaemic (persistent high level of glucose in blood) and will be diagnosed with type 2 diabetes[89].

Insulin with the help of enzyme phosphatidylinositol (PI) 3-kinase prevent the process of atherogenesis. PI 3- kinase pathway is impaired in case of insulin resistance and the Insulin lost its anti-atherogenic properties[90]. Among the various reasons of Insulin

resistance, abdominal obesity is one of the main reasons among them. The adipose tissues are release Nonesterified fatty acids (NEFA) in excess, which aggravates the insulin resistance. Insulin resistance causes increased lipolysis from the fatty tissue which increases the level of free fatty acids and subsequently inhibiting the anti-lipolytic effect of Insulin[89]. Visceral or omental fat consider to be the most injurios and contributes in most to the processes of generation of lipotoxicity in peripheral tissues by the secretion of adipo-cytokines (including cytokines, acute phase reactants, growth factors, and other inflammatory mediators)[91]. Metabolic Syndrome is associated with a there is high amount of intra-abdominal fat, low adiponectin levels (direct role on fat metabolism, anti diabetes, anti artherogenic & anti- inflammatory in action), and the increased levels of cytokines (interleukin 1RA and interleukin 1beta)[92]. Hyperinsulinemia may potentiates the production of very low-density lipoprotein triglycerides and thus raise triglycerides. Thus even before the establishment of the diagnosis of diabetes mellitus, in such type of patients, there is continuous damage occurring to the body, like triglyceridemia which further impairs insulin sensitivity. Insulin resistance can also raise blood pressure[93].

Since insulin resistance in such individuals increases the risk of developing cardiovascular disease and Type 2 diabetes, the several researchers have proposed measures of insulin resistance in obese individuals with and without Metabolic Syndrome. Hence the insulin assays or alternative biomarkers of insulin resistance may facilitate cardiovascular risk prediction in individuals with Metabolic Syndrome[94].

Central obesity

According to recent criteria IDF introduced a new term for metabolic syndrome as 'central obesity syndrome'[95]. The main clinical importance of the term metabolic syndrome is that it helps for early detection of people at risk of cardiovascular disease and Type 2 Diabetes [96]. There is association between obesity with insulin resistance and the metabolic syndrome. Obesity predispose to hypertension, hyper- cholestremia, low level of HDL-c, hyperglycemia, and is also independently associated with higher CVD risk[97-100]. The portal circulation directly receives the harmful metabolic product from omental/ visceral fat and transports it straight to liver. Therefore lot of free fatty acids first accumulates into the liver and gradually in pancreas, heart, and other organs. These results into organ dysfunction impaired Glucose tolerance, high levels of blood sugar, high cholesterol and abnormal cardiac functions. This effect is known as lipotoxicity[101]**.**

The evaluation of abdominal obesity can be done by using computed tomography (CT) or magnetic resonance imaging (MRI) to access the amount of visceral fat. The risk of dangerous health consequences like type 2 diabetes mellitus, coronary artery disease (CAD) and a wide range of other conditions, including some variety of cancer shown higher association with increase in body mass index (BMI), which has been widely discussed by many researchers[102], thus the weight reduction at that point could be the best possible way to prevent it. But in case of metabolic syndrome the truncal obesity, which is simply measured by waist circumference, is better indicator of the metabolic syndrome profile than BMI[103-105]. Few researchers suggested that Index of central obesity, which is the ratio of waist circumference and height, was a better substitute than the widely used waist circumference[106].

Hypertension

Hypertension one of the main component of metabolic Syndrome and may remain silent and undetected for very long period. As obesity it is also an important risk factor alone for development of cardiovascular disease. All the hemodynamic and metabolic disorders are closely associated with both essential hypertension and insulin resistance. Many metabolic abnormalities like obesity, glucoseintolerance, and dyslipidemia are the most commonly associated with Essential hypertension[107]. Obesity is one of the main risk factor for uncontrolled hypertension, as mentioned many Studies have shown that obesity is interlinked between hypertension, insulin resistance and dyslipidemia[97]. In another study these components were found in the clustering of metabolic variables. Both general and central obesity predisposed to insulin resistance and hypertension and only weakly linked to yslipidemia[83]. The results of Farmingham Heart Study estimate the risk of overweight and obesity was the cause of hypertension in 78% of males and 65% of females [108]. Many Studies showed that hyperglycemia and insulin both can activate the RAS (Renin-Angiotensin System) by increasing the expression of angiotensinogen, Angiotensin- II, and the T1 receptor, which, may contribute to the development of hypertension in patients with insulin resistance[109]. Many researchers have disscussed the RAS and insulin signaling at multiple levels, and the role of RAS has belived to be important for atherogenesis. The activation of RAS may block the action of Insulin via the PI3 pathway[110]. Many evidences support the association between hypertension and obesity in which the role of insulin and leptin as well as sympathetic nervous system may be involve. Leptin and insulin are assumed to be compensatory mechanisms required to restore energy balance with sympathetic nervous system as one of the effector arms[111].

Dyslipidemia

A study in 2001, reported the correlation between fasting lipids, HbA1c in the persons with diabetes and suggested a poorer glycemic control with dyslipidemia in type 2 diabetes mellitus [112]. Similarly Another study showed the presence of small, dense LDL particles may be associated with an increase of subsequently developing Ischemic heart disease[113]. LDL particle size showed no correlation with the LDL cholesterol, but it is strongly related with triglyceride and HDL cholesterol levels and with the cholesterol: HDL cholesterol ratio. The high level of triglycerides and low levels of HDL cholesterol are found in Metabolic Syndrome. In pre-diabetic condition as in metabolic syndrome, the circulating free fatty acids result in the formation of triglycerides.

Sniderman et. al. in 2003 approaches to lipid-lowering treatment in persons with diabetes presented the analysis of triglyceridemia and elevated level of apo B and was concluded that the real target in the treatment for diabetes should be apo B rather than LDL cholesterol. Without measurement of apoB molecule, it is difficult to distinguish with triglyceridemia and large particles in the patient those apoB is normal[114].

ProInflammatory state

It was noted, that low-grade inflammation is associated with insulin resistance and endothelial dysfunction. The adipose tissue liberates toxic inflammatory cytokines that may

leads to insulin resistance with vascular disease. The adipocyte-generated inflammatory cytokines originates the inflammatory reactions and endothelial dysfunction, which strongly correlate with insulin resistance[115]. Circulating signals from fat include Free Fatty Acids, adiponectin, IL-6 (particularly at the liver, where IL-6 increases CRP production), resistin, leptin, and TNF-α. Various studies also co-relate the levels of C-reactive protein and interleukin-6 to markers of the insulin resistance syndrome and of endothelial dysfunction as occur in obesity and chronic infections. The Metabolic syndrome and abdominal obesity are act like stress and leads to activation of inflammatory pathways, causation of inflammation are multifactorial. The inflammatory process in metabolic syndrome is of low grade chronic inflammation and not related to any infection, autoimmunity or massive tissue injury. Some Researchers termed this inflammatory condition as 'Metaflammation', it means metabolically triggered inflammation. A few studies have corelated the strong association between obesity and inflammatory markers, mainly CRP (C – reactive protein) in females[116], but also other inflammatory markers for both female and male[117].

The obese person having increase concentration of inflammatory mediators, such as, CRP (C-reactive protein), TNF- α (tumor necrosis factor-alpha), IL-6 (interleukin-6) and others. Adipose tissue is mainly express most of these inflammatory markers. Obesity is the most important condition associated with C-reactive protein[118].

Prothrombotic state

The metabolic syndrome is associated with increased plasma level of plasminogen activator inhibitor (PAI)-1 and fibrinogen, which characterize prothrombotic state. The pro-thrombotic and pro- inflammatory states seems to be metabolically interrelated, this is because the Fibrinogen (acute-phase reactant like CRP) rises in response to a high-cytokine state[93].

The study of plasminogen activator inhibitor-1 shows the association between hemostatic markers and metabolic syndrome**.** A study was done to determine whether plasma concentrations of thrombin- activatable fibrinolysis inhibitor (TAFI) in the patients with type 2 diabetes mellitus were associated with components of metabolic syndrome and also for the high-sensitivity C-reactive protein (hs- CRP), plasminogen activator inhibitor (PAI)-1, and LDL cholesterol[119]. The result revealed the strong correlation between LDL cholesterol and plasmaTAFI with type 2 diabetes mellitus. The acceleration of inflammation, inhibition of fibrinolysis and high level of TAFI and PAI-1 is mainly due to Co-existence of metabolic syndrome and hypercholesterolemia. PAI-1 is consider as an important risk factor for metabolic syndrome. Thus the 4 biomarkers, PAI-1 along with Three other biomarkers, CRP, IL6, and fibrinogen contribute in the metabolic syndrome risk assessment[120].

Genetics of Metabolic Syndrome

There is differing opinion and very less studies have done on effects of genetic variation of metabolic syndrome. The proposed candidate genes for metabolic syndrome that, often support the thrifty phenotype are involved in energy storage[121]. Some persons are energy storing genetic variants, when they expose to the westernized environment and excess of high calorie food and sedentary life style, they may have chance to become

detrimental and cause the phenotype with metabolic disturbances observed in metabolic syndrome, including obesity and glucose intolerance. Clustering of genes in families suggest a genetic component. The genes of genetic varient persons have various common variants which influence fat and glucose metabolism along with environmental factors, which can increase the susceptibility to the syndrome. The genes for β3- adrenergic receptor, hormone-sensitive lipase, lipoprotein lipase, IRS-1, PC-1, skeletal muscle glycogen synthase, etc. are increases the risk of the metabolic syndrome. Genome-wide searches have added an extra benefit by identifying the genes. Genes regulating lipolysis and thermogenesis still remain prime candidates Among genes contributing to the metabolic syndrome[122]. Till date, there is no unifying genetic factors have been clearly identified who predispose to metabolic syndrome. Several genes have been shown association with at least two factors of metabolic syndrome, so they are consider to be most suitable candidate genes. As, adrenergic beta receptors (ADRB1, ADRB2 AND ADRB3) have found to be associated with obesity, hypertension and glucose intolerance, they are considered to be good candidates for predisposing to development of Metabolic syndrome[123,124]. For example in Chronic stress there is dysregulation of HPA axis/ ANS and Metabolic syndrome. The chronic hypersecretion of stress mediators, such as cortisol, in individuals with a genetic predisposition exposed to a permissive environment, may cause visceral fat accumulation as a result of chronic hypercortisolism, low secretion of growth hormone and hypogonadism[125,126]. Moreover, hypercortisolism directly reslults insulin resistance of peripheral target tissues in proportion to glucocorticoid (GC) levels and a particular target tissue's sensitivity to them as shown by studying polymorphisms of the glucocorticoid receptor gene[127]. These alterations in hormone level may cause to reactive insulin hypersecretion, and increase in visceral obesity and sarcopenia, resulting to dyslipidemia, hypertension and DMT2 [128].Several genes have shown their biological relevance, like, genes in systems of energy balance, nutrient partitioning, lipid and insulin metabolism, lipolysis, thermogenesis, fuel oxidation, and glucose uptake in skeletal muscle of the potential candidate. Association of several genes with metabolic syndrome has been considered in various ethnic populations. These candidate genes includes peroxisome proliferator - activated receptor (PPAR γ), adiponectin, CD36, β -adrenergic receptors, insulin receptor substrates (IRS), 11 β- hydroxysteroid dehydrogenase type 1 (11β-HSD1), CRP, tumor necrosis factor-α (TNF-α), calpain-10 (CAPN10), upstream transcription factor 1, and skeletal muscle glycogen synthase and many other genes[129]. There are still an ongoing discussions and controversies as remains in genetic era, as varoius genome wide linkage studies for Metabolic syndrome and its components have been made to identify few chromosomal regions displaying linkage to Metabolic syndrome and its components. But there is not a single susceptible gene for metabolic syndrome has been identified till date [120,130]**.** Apart from the above mentioned conditions, the another system, the circadian CLOCK system may also be implicated in the pathogenesis of Metabolic syndrome. Interestingly, most of the metabolic phenotypes related with dysregulation of the CLOCK system and the HPA axis overlap[131].

Metabolic Risk Factors

The primary goal of metabolic syndrome management is to minimize the risk of Atherosclerotic cardiovascular disease and Type 2 DM. The principal way to achieve this goal is to apply lifestyle interventions that target lifestyle risk factors such as obesity, physical

inactivity, atherogenic diet, and smoking. Regardless of Atherosclerotic cardiovascular disease risk, all people with metabolic syndrome are candidates for lifestyle intervention. Metabolic risk factors such as atherogenic dyslipidemia, elevated blood pressure, or prediabetes can be improve by lifestyle interventions. If metabolic syndrome is present in patients with existing Atherosclerotic cardiovascular disease or diabetes, lifestyle strategies and pharmacologic therapies should be applied according to present guidelines to decrease complications associated with these conditions.

Risk Assessment

Determining the best pharmaco-therapeutic approach for patients with metabolic syndrome is dependent on the known or estimated risk of Atherosclerotic cardiovascular disease, which may be widely variable among patients who meet criteria for metabolic syndrome. For such patients, the Framingham risk assessment tool (http://cvdrisk.nhlbi.nih.gov/calculator.asp*)* can be used to predict a patient's 10-year risk of coronary heart disease (CHD). The Framingham risk assessment tool (table -2) quantifies this risk and provides guidance for the appropriate treatment goals for these patients. Table provides metabolic syndrome treatment goals based on Framingham risk.

Table -2: Treatment Goals Based on Framingham Risk for Patients (Without Existing Disease)[87, 133-135]

S.No.	Framingham Risk (%)	Blood Pressure (mm Hg)	LDL-C (mg/dL)	Non–HDL-C (mg/dL)	FPG (mg/dL)	Aspirin
1	**< 10**	**< 140/90**	**< 160①, < 130①**	**< 190②, < 160②**	**< 100**	**Consider③**
2	**10–20**	**< 130/80**	**< 130, < 100④**	**< 160, < 130④**	**< 100**	**Yes**
3	**> 20**	**< 130/80**	**< 100, < 70⑤**	**< 130, < 100⑤**	**< 100**	**Yes**

FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol

① Goal less than 160 mg/dL for patients with 0 or 1 major risk factor (i.e., cigarette smoking, hypertension, low HDL-C, premature coronary heart disease, or age); goal less than 130 mg/dL for patients with two or more major risk factors.

② Goal less than 190 mg/dL for patients with 0 or 1 major risk factor; goal less than 160 mg/dL for patients with two or more major risk factors.

③ Some patients with metabolic syndrome will meet criteria according to the U.S. Preventive Services Task Force statement concerning the use of aspirin for the prevention of cardiovascular disease.

④ Multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), or metabolic syndrome.

⑤ Established coronary heart disease plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, or recent acute coronary syndrome.

Treatment of Metabolic Syndrome

Once metabolic syndrome is diagnosed, the aggressive and strict management of the condition should be started as shown in figure 2. The aim of treatment is to reduce the risk of CVD and type 2 diabetes. The full cardiovascular risk assessment (including smoking status) of the Patients of Metabolic syndrome should be carried out.

Primodial Prevention

The insulin resistance, physical inactivity and excess weight are the main risk factors to the development of Metabolic Syndrome, and all the risk factors are preventable. The best way to stop developing Metabolic Syndrome is to check before it starts. So exercise and weight loss can help to reduce or prevent the complications associated with this condition. The slight changes in eating habits and addiction can prevent the development of insulin resistance but is probably more difficult, as it may require.

Prevention of Insulin Resistance

The best way is to avoidance of those foods which promote insulin resistance. It means avoidance of refined sugar, white flour products, simple carbohydrates, etc. Maintain normal weight, balanced diet, and regular cardiopulmonary exercises are the best preventive measures. Lots of dietary fiber consumption is also helpful, as fiber delays the absorption of sugar from food into the blood stream.[137]

Benefit of Weight Reduction

Only 5 – 10% of total body weight loss can restore the body's ability to recognize insulin and reduce the chances of the metabolic syndrome.[137]

Exercise

Only increased activity can show the improvement of insulin levels. Cardiopulmonary exercises such as Aerobic exercise, brisk walking for 30-minute everyday can result in weight loss, improvement in blood pressure, improvement in cholesterol levels and a decrease the risk of developing diabetes and may also reduce the risk for heart disease even if without significant weight loss. [137,138]

Dietary modification

Metabolic Syndrome is majorly a nutritional disease. It can be managed with dietary modifications, low carbohydrate diet or reduced intake of sweets, pastas and breads, and replacement of carbohydrates with good fats (especially Essential Fatty Acids). The intake of balance diet is very important for this syndrome. [137,138]

Role of Dietary Fats

Switching to the right balance of dietary fats is most important as the wrong kinds of fats can lead to insulin resistance by interfering with the metabolism of glucose and increasing insulin resistance. Including cold-water fish two times/week, flax seeds and nuts (such as walnuts, Brazil nuts, etc.) in the diet, and having dark green and leafy vegetables helps to restore the omega-3 to -6 balance, important in the prevention of insulin resistance. Omega-3 fatty acids helps to maintain flexibility of cell membranes, which is important because only healthy membranes contain large numbers of insulin receptors and increasing the surface areas available for insulin binding. The daily recommendation for

omega-3 fatty acid is about 4,000 mg (4 grams) has shown helpful to prevent Metabolic Syndrome[139].

Limit Alcohol Intake and cessation of smoking

Some recent studies suggest that consumption of alcohol in moderate amount help to prevent Metabolic Syndrome but limit in alcohol intake is a better choice. Drinking excess of alcohol can increase blood pressure and triglyceride levels, and also harm the liver, brain and heart. The other part is that, the alcohol is a source of empty calories, which can lead to weight gain instead of weight loss. The recommendation for alcohol drinking is, one drink in a day for women or two drinks for men**.** Middle-aged and elderly smokers were at approximately 4-5 times higher risk among Metabolic Syndrome subjects [141], therefore, the complete cessation of cigarette smoking is advisable. [137, 138]

Primary prevention

The major goal of the treatment is for the both underlying cause and the cardiovascular risk factors if they persist in a particular. The most of the people with Metabolic Syndrome are over- weight and leading a sedentary lifestyle, so the preferred initial treatment is lifestyle modification. The diet and exercise program for weight reduction. Our allopathic medical care system typically depends on pharmacotherapy, but there are also some suggestions for supplementation.

Diet

In general terms, a well-balanced diet is high in whole foods and low in sugars and saturated fats are good initiatives. A high fiber diet helps to balance blood sugar, therefore vegetables, nuts, seeds and whole grains should be encouraged. Protein also helps to balance blood sugar level, so viable sources of vegetable protein (or lean animal protein) with each meal or as snacks is also good for heath. Frequent small meals throughout the day are consider better than 3 large meals, as they keep the blood sugar and insulin levels in steady state. Sugars, white flour products, alcohol, caffeine and sources of saturated fat is advise to avoid. These spikes of insulin, blood sugar and saturated fat levels, increase the risk of diabetes and heart disease. Also advise to avoid artificial sweeteners, trans- fats and high-glycemic load foods. The new trend of diet as, Mediterranean diet – rich in “good” fats (olive oil) and contains a suitable amount of carbohydrates and proteins (as in fish and chicken). The study on the people who are on the Mediterranean diet as compared to a low fat diet, the people on the Mediterranean diet[140] have a greater decrease in body weight, and also had better improvements in blood pressure, cholesterol levels, and other markers of heart disease. These all are the components of Metabolic Syndrome[137,138]

Exercise

A daily sustainable exercise program is a main component in non- pharmacological treatment of Metabolic Syndrome (if no medical contraindication). The blood pressure, cholesterol levels, and insulin sensitivity is benefited by exercise, regardless of whether weight loss is achieved or not. [137,138]

Chromium

Improves glucose tolerance and balances sugar levels in the blood. Up to 1,000 mcg to be taken as daily dose.[142]

Magnesium

The Magnesium also play a important role in both the prevention and treatment of Metabolic Syndrome and diabetes. It increases the number and sensitivity of insulin receptors. A dose is 500-1,500 mg daily of magnesium bound to succinate, citrate, or aspartate. The loose stool may occur with lager dose of Magnesium oxide.[143]

Gymnema sylvestre

An herb which found in the tropical forests of southern and central part of India, it decreases the blood sugar levels. The daily recommended dose is 400 mg of a 25% gymneic acid extract[144].

Alpha lipoic acid

Some researchers belive the alpha-lipoic acid is the principal supplement for preventing and reversing Metabolic Syndrome. The main action of this supplement is increasing the burning of glucose. The body requires the alpha-lipoic acid to produce energy and plays a crucial role in the energy-producing structures, like mitochondria in the cells. The body can make enough alpha-lipoic acid for the basic function. Alpha-lipoic acid when present in excess, remains in free state in the cells, acts as an antioxidant. Alpha-lipoic acid helps in deactivation of free radicals which mainly cause cell-damaging in many bodily systems and also improves insulin sensitivity. Some researchers believe the low dose as 50-250 mg /day in compare with other antioxidants may be sufficient to prevent Metabolic Syndrome. However, the typical dose is 300-1,800 mg daily[145].

Vanadyl sulfate

Vanadyl Sulfate is most popular form of vanadium, an element in the body. Mainly found in foods such as pepper, dill, radishes, eggs, vegetable oils, buckwheat, and oats. Recently noticed by the researchers that it improves glucose tolerance in people with insulin resistance by insulin - mimicking activities. The daily recommneded dose is 100-300 mg[146].

Biotin

Biotin associated with proper glucose metabolism. Daily dose is 9-16 mg daily[147].

High-potency multivitamin/ mineral supplement

This will supply many of the nutrients involved with blood glucose metabolism[148].

Essential Fatty Acids

Essential Fatty Acids especially omega-3 fatty acids are essential to health and insulin function. Flax seed or fish oil having high content of EFAs. Daily required dose is up to 9 grams (9,000 mg) in divided doses[139].

Bitter melon

***Momordica charantia* (bitter melon)** can help in balancing blood-sugar levels. The 200 mg three times daily is the recommended dose[149].

Garlic

An important commonest used herb is for stabilizing blood sugar, and for reducing the risk of heart disease and other circulatory disorders. It improves blood flow, lower blood pressure, and decrease cholesterol levels. Recommended minimum dose is 300-450 mg twice daily[150, 151].

Fenugreek

This herb also stabilizes blood sugar levels. The dose is 15-50 grams daily[152, 153].

Pharmacotherapeutic approach

The high risk of cardiovascular disease is considered in those patients whose lifestyle changes are not up to the mark, so pharmacotherapy may be needed to treat metabolic syndrome. The treatment could modulate the underlying mechanisms of the metabolic syndrome, which decrease the impact of all the risk factors and long term complications associated with it. However, these mechanisms are still not clear and therefore specific drug treatment is not available till date. The drugs given in this condition is mainly for to lower the individual risk associated with each component and to reduce the overall impact on Cardiovascular disease and diabetes risk.

Dyslipidemia

Primary aims for therapy:

- Decrease the triglyceride levels, as well as lowering ApoB and non-HDL cholesterol
- Increase HDL-c levels
- Lower LDL-c levels, elevated levels represent a high risk in the metabolic syndrome

Pharmacotherapeutic Options:

- Fibrates, a PPAR alpha agonists, which improve all the components of atherogenic dyslipidemia and appear to reduce the Cardiovascular disease risk in the people with metabolic syndrome. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) revealed that raising HDL-c concentrations using a fibrate in patients

with well-established IHD and both a low levels of HDL-c and a low levels of LDL-c will significantly reduce the incidence of major coronary events.[154]

- Statins to lower all ApoB-containing lipoproteins and to achieve ATP III goals for LDL-c as well as for non-HDL-c (ATP III, 2001). Many clinical studies have confirmed the benefits of statin therapy .[155-157]
- Fibrates may combine with statins, but complicated by side effects.

Elevated blood pressure

- According to the USA Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) recommendations, BP ≥ 140/≥ 90 mm Hg consider as hypertension and should be treated.[158]
- In known diabetic patient, antihypertensive therapy should be started at BP ≥\130/ ≥ 80 mm Hg.

Pharmacotherapeutic Options:

- As per various clinical trials, the people with diabetes, the most useful antihypertensive drugs are Angiotensin converting enzyme inhibitors and angiotensin receptor blockers[163]. At this time, however, the majority of suggest that the risk and reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug. The recommendation of guidelines to avoid isolated or combined administration of diuretics or beta- blockers in patients who predisposed to diabetes such as metabolic syndrome[162] or a blood glucose in the glucose intolerance range, i.e., between 100 – 125 mg./ dl.[158-161]
- Not a single agent has been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

Insulin resistance and hyperglycemia

There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce cardiovascular disease risk when metabolic syndrome is present. The Diabetes Prevention Program (DPP) showed that metformin therapy in people with prediabetes will prevent or delay the development of diabetes164-166. Some literature suggests that metformin may help to reverse the pathophysiological changes of metabolic syndrome. This includes when it is used in combination with lifestyle changes or with peroxisome proliferator-activated receptor agonists, such as fibrates and thiazolidinediones, each of which may produce favorable metabolic alterations like delaying or preventing type 2 diabetes in people with impaired glucose tolerance (IGT) and insulin resistance as single agents in patients with metabolic syndrome.167-170 Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in people with IGT. 171-172.

Data do not yet exist to show whether any of the currently available thiazolidinediones reduce the risk of Cardiovascular disease in those with the metabolic syndrome, IGT or diabetes.

Surgical considerations

There was no surgical interventions for metabolic syndrome have been widely accepted till today But trials of bariatric surgery in patients who were morbidly obese and had metabolic syndrome suggested beneficial results, including decreased insulin resistance and lower levels of inflammatory cytokines.[173,174]

Importantly, metabolic syndrome raises specific perioperative issues that should be considered in patients with metabolic syndrome undergoing any major surgical procedure.[175]

CONCLUSION

The term "Metabolic Syndrome" is a indicator to identify individuals at high risk for the development of cardiovascular disease and diabetes. Its contributory factors are obesity, impaired glucose metabolism, dyslipidemia, and hypertension. The IDF and AHA/ NHLBI criteria is the most suitable for practical use in clinical medicine. The Insulin resistance is one of the major risk factors defining metabolic syndrome precedes type 2 diabetes, and can itself be an important condition requires treatment. The Persistent increased levels of insulin and glucose are linked to many dangerous changes to the body, including:

1. Injury to the endothelial lining of coronary and other arteries, leads to the development of vascular heart disease or stroke.
2. Alteration in the kidney ability to remove salt, leads to high blood pressure, heart disease and stroke.
3. High levels of triglyceride, resulting in great risk of developing cardiovascular disease.
4. High risk of blood clot formation, which leads thromboembolic conditions like myocardial infarction and strokes.
5. Insulin resistance which leads to glucose intolerance and type 2 diabetes, can further increase risk for a heart attack or stroke and other diabetes related complications.

Various strategies have been proposed to prevent the development of metabolic syndrome at initial stage like Simple life style modifications specially weight reduction, regular exercise, diet modification, decreasing the effect of insulin resistance by these modifications or drug treatment is promising in decreasing the risk of CVD and type 2 diabetes.Once metabolic syndrome is diagnosed, the aggressive and strict management of the condition should be started. The individual disorders that compose the metabolic syndrome should be treated separately. The increasing awareness of the pathophysiology, the risk factors and methods of prevention should be emphasized to formulate treatment strategies for prevention of the disease.

ISSN: 0975-8585

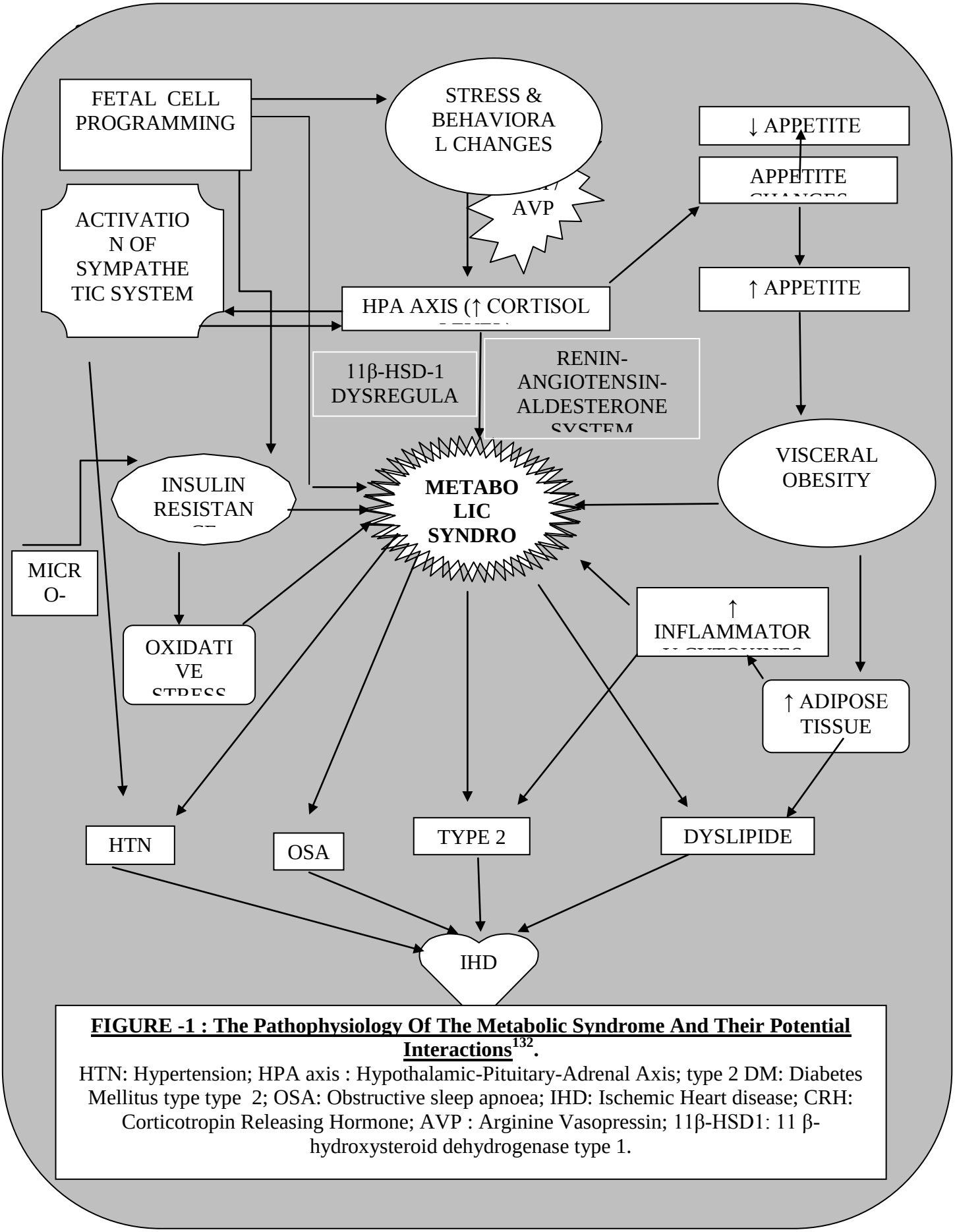
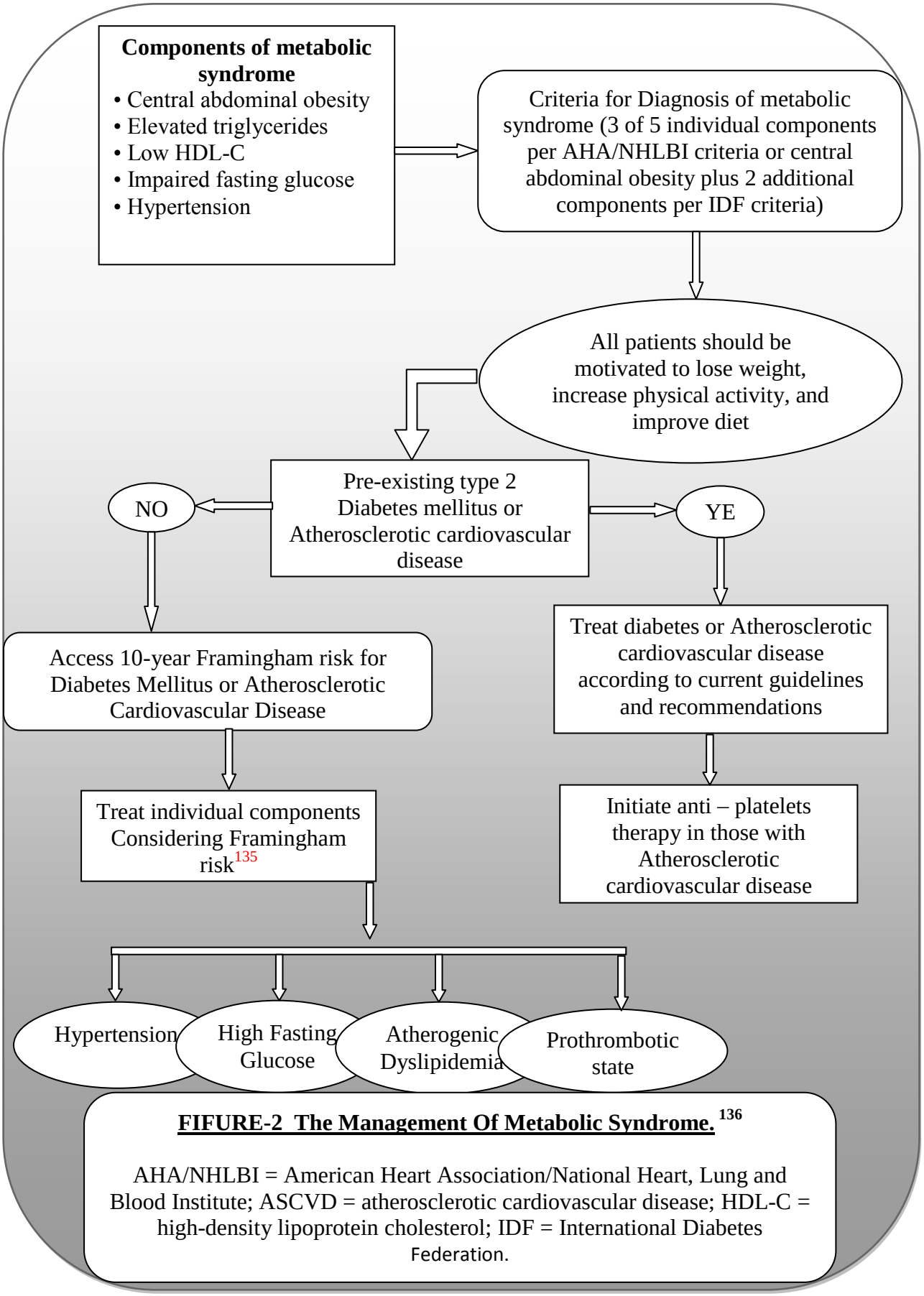


FIGURE -1 : The Pathophysiology Of The Metabolic Syndrome And Their Potential Interactions[132].

HTN: Hypertension; HPA axis : Hypothalamic-Pituitary-Adrenal Axis; type 2 DM: Diabetes Mellitus type type 2; OSA: Obstructive sleep apnoea; IHD: Ischemic Heart disease; CRH: Corticotropin Releasing Hormone; AVP : Arginine Vasopressin; 11β-HSD1: 11 β-hydroxysteroid dehydrogenase type 1.

ISSN: 0975-8585



FIFURE-2 The Management Of Metabolic Syndrome. [136]

AHA/NHLBI = American Heart Association/National Heart, Lung and Blood Institute; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation.

ISSN: 0975-8585

ACKNOWLEDGEMENT

I am deeply indebted to my Professor and HOD, Dr Sudhanshu Sekhar Mishra, who gave the idea about this review and guided me all through the process of drafting this manuscript.

REFERENCES

[1] Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB: The metabolic syndrome:prevalence and associated risk factor findings in the US population from the Third National Health and NutritionSurvey, 1988-1994. Arch Intern Med 2003, 163:427–436.

[2] Katzmarzyk P, Church T, Janssen I, Ross R, Blair S.Metabolic Syndrome, obesity and mortality. Diabetes Care 2005, 28: 391–397.

[3] Reaven G, Role of insulin resistance in human disease. Diabetes 1988, 37, 1595–1607.

[4] Wilcox I, McNamara SG, Collins FL et al. “Syndrome Z”: the interaction of sleep apnoea, vascular risk factors and heart disease.Thorax 1998; 53(Suppl 3):25–28.

[5] Nock NL, Li L, Larkin EK, Patel SR, Redline S. Empirical evidence for “syndrome Z”: a hierarchical 5-factor model of the metabolic syndrome incorporating sleep disturbance measures. Sleep 2009; 32 : 615-22.

[6] Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004; 350, 2362-2374.

[7] Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988- 1994. Arch Pediatr Adolesc Med 2003; 157, 821-827.

[8] Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. J Clin Endocrinol Metab 2004; 89, 108-113.

[9] Crepaldi G., Maggi Stefania, The metabolic syndrome: a historical context. Diabetes Voice 2006, (51), may 2006.

[10] Paulescu N, Traité de Physiologie Médicale, 1920, vol 2,Cartea Românească.

[11] Avogaro P, Crepaldi G, Enzi G, et al. Associazione di-iperlipemia, diabete mellito e obesità di medio grado. Acta diabetol Lat 1967; 4: 36-41.

[12] Moga A., Hărăguş S, Ateroscleroza. Ed. Academiei Române, Bucureşti, 1970.

[13] Moga A., Orha I. , Stăncioiu N., Vlaicu R, Cardiopatiile cronice majore. Factori de risc şi perioada deconstituire. Ed. Academiei Române, Bucureşti, 1974.

[14] Karassi A., Infarctul miocardic acut. Ed Medicală, Bucureşti, 1979.

[15] Haller H, Hanefeld M. Synoptische Betrachtung metabolischer Risikofaktoren. Haller H Hanefeld M Jaross W eds. Lipidstoffwechselstörungen 1975:254-264.

[16] Haller H. "Epidermiology and associated risk factors of hyperlipo-proteinemia". Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete, April 1977; 32 (8): 124–8. PMID 883354.

[17] Ionescu-Tîrgovişte C., Tratat de Diabet Paulescu, Ed. Academei Române, 2004, 727–749.

[18] Zimmet P, Serjentson S, The epidemiology of diabetes mellitus and its relantionship with cardiovascular disease. New Apect in diabetes, Ed. Lefebvre & Standl, de Gruyer, Berlin, 1992, 5–22.
[19] Morris DH et al. Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia 2013;56:1489-1493.
[20] World Health Organization, Report of a WHO consultation: definition of metabolic syndrome in definition, diagnosis and classification of diabetes mellitus and its complications. Part I: Diagnosis and classification of diabetes mellitus, 1999.
[21] Bjőrntorp P, Do stress reactions cause abdominal obesity and comorbidities?. Obesity Reviews, 2001, 2,73–86.
[22] Balkau B, Charles M.A, The European Group for the Study of Insulin Resistance (EGIR): Comment on the provisional report from the WHO consultation. Diabet Med 1999, 16, 442–443.
[23] Brunner E.J et al., Social inequality in coronary risk: Central obesity and the metabolic syndrom.Diabetologia, 1997, 40, 1341–49.
[24] National Cholesterol Education Program (NCEP),Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel ondetection, evaluation, and treatement of high blood chol sterol in adults (Adult Treatement Panel III). JAMA 2001, 285, 2486–97.
[25] American College of Endocrinology: Insulin resistance syndrome (Position Statement), Endocr Pract 2003, 9 (Suppl.2), 9–21.
[26] International Diabetes Federation Epidemiology Task Force Consensus Group. The IDF Consensus worldwide definition of the metabolic syndrome. International Diabetes Federation Brussels: 2005 (available at: www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf).
[27] Alberti K.G.M., Eckel Robert H., Grundy Scott M., Zimmet Paul Z., Cleeman James I., Donato Karen A., Fruchart Jean-Charles, James W. Philip, Loria Catherine M., Sidney C. Smith Jr, Harmonizing the Metabolic Syndrome: A joint Interim Statement of the Internatonal Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 2009,120; 1640–1645.
[28] The IDF consensus worldwide definition of the metabolic syndrome. [Last accessed on 2011 June 11]. Available from: www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.
[29] Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am. 2004;33(2):351-375, table of contents.
[30] Nakagami T, Qiao Q, Carstensen B, Nøhr-Hansen C, Hu G, Tuomilehto J, Balkau B, Borch-Johnsen K. The DECODE-DECODA Study Group. Age, body mass index and Type 2 diabetes—associations modified by ethnicity. Diabetologia, 2003;46:1063–1070.
[31] Saad MF, Lilloja S, Nyomba BL et al. Racial differences in the relation between blood pressure and insulin resistance. N Eng J Med, 1991; 324:733–739 2 Epidemiology of the Metabolic Syndrome 13.

[32] Lee CM, Huxley RR, Woodward M et al. The metabolic syndrome identifies a heterogeneous group of metabolic component combinations in the Asia-Pacific region. Diabetes Res Clin Pract, 2008; 8:377–380.
[33] Freedman DS: Obesity - United States, 1988–2008. MMWR Surveill Summ 2011, 60 (Suppl) :73-77.
[34] Ogden CL, Carroll MD, Kit BK, Flegal KM: Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief 2012, 1-8.
[35] Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al.: National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants.Lancet 2011, 377:557-567.
[36] Kelly T, Yang W, Chen CS, Reynolds K, He J: Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008, 32:1431-1437.
[37] Hiram Beltrán-Sánchez et.al. Prevalence and Trends of Metabolic Syndrome in the Adult U.S. Population, 1999–2010. J Am Coll Cardiol. 2013;62(8):697-703. doi:10.1016/j. jacc. 2013.05.064.
[38] Van Vliet-Ostaptchouk et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies BMC Endocrine Disorders 2014, 14:9
[39] Wichmann HE, Gieger C, Illig T: KORA-gen–resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 2005, 67(Suppl 1):S26–S30.
[40] Inouye M, Kettunen J, Soininen P, Silander K, Ripatti S, Kumpula LS, et al: Metabonomic, transcriptomic, and genomic variation of a population cohort. Mol Syst Biol 2010, 6:441.
[41] Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, et al: Cohort profile: the HUNT study, Norway. Int J Epidemiol 2013, 42:968–977.
[42] Pattaro C, Marroni F, Riegler A, Mascalzoni D, Pichler I, Volpato CB, et al: The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. BMC Med Genet 2007, 8:29.
[43] de Carvalho Vidigal et al. Prevalence of metabolic syndrome in Brazilian adults: a systematic review BMC Public Health 2013, 13:1198
[44] Lydia U. Kaduka et al. Prevalence ofMetabolic Syndrome Among an Urban Population in Kenya, Diabetes Care 2012; 35:887–893.
[45] Trevor S Ferguson et al. Prevalence of the metabolic syndrome and its components in relation to socioeconomic status among Jamaican young adults: a cross-sectional study, BMC Public Health 2010, 10:307 doi:10.1186/1471-2458-10-307.
[46] Anthonia O Ogbera et al. Prevalence and gender distribution of the metabolic syndrome, Diabetology & Metabolic Syndrome 2010, 1758-5996.
[47] Xiang Qian Lao et al. Dramatic escalation in metabolic syndrome and cardiovascular risk in a Chinese population experiencing rapid economic development, *BMC Public Health* 2014, 14:983 doi:10.1186/1471-2458-14-983.
[48] Sidorenkov et al. Prevalence of the metabolic syndrome and its components in Northwest Russia: the Arkhangelsk study, *BMC Public ealth* 2010, 10:23 doi:10.1186/1471-2458-10-23.

[49] F. Sharifi et al. Prevalence of Metabolic Syndrome in an Adult Urban Population of the West of Iran Experimental Diabetes Research Volume 2009, Article ID 136501, 5 pages doi:10.1155/2009/136501
[50] DR Kang et al. Prevalence and Associated Risk Factors of the Metabolic Syndrome in the Korean Workforce, Industrial Health 2013, 51, 256–265.
[51] Ayesha a. Motala, Tonya Esterhuizen, Fraser J. Pirie, Mahomed A.K. Omar, To determine the prevalence of metabolic syndThe Prevalence of Metabolic Syndrome and Determination of the Optimal Waist Circumference Cutoff Points in a Rural South African CommunityDiabetes Care 2011; 34:1032–1037.
[52] Mitsuyoshi urashima et al. Prevalence of metabolic syndrome in a 22,892 Japanese population and its association with life style JMAJ 2005; 48(9): 441- 450.
[53] Katulanda et al. Metabolic syndrome among Sri Lankan adults: prevalence, patterns and correlates Diabetology & Metabolic Syndrome 2012, 4:24.
[54] Niloufer Sultan Ali et al. Retrospective Analysis of Metabolic Syndrome: Prevalence and Distribution in Executive Population in Urban Pakistan International Journal of Family Medicine 2012; Article ID 649383: 8
[55] Madiha Ahmad et al. Prevalence of various components of Metabolic Syndrome in our Young Population Pak J Physiol 2011;7(2).
[56] Bhat et al. Prevalence of the Metabolic Syndrome among North Indian Adolescents Using Adult Treatment Panel III and Pediatric International Diabetic Federation Definitions J Diabetes Metab 2014, 5:3.
[57] Pathania, et al.: Epidemiological study of metabolic syndrome in a rural area of Ambala district, Haryana, Journal of Family and Community Medicine 2014; 8(21):2:130-133.
[58] Seerat Hussain Beigh at al. Prevalence of metabolic syndrome and gender differences Bioinformation 2012; 8(13): 613-616.
[59] Sawant et al. Prevalence of Metabolic Syndrome in Urban India, Cholesterol 2011; Article ID 920983:7. doi:10.1155/2011/920983
[60] Prasad DS, Kabir Z, Dash AK, Das BC. Prevalence and risk factors for metabolic syndrome in Asian Indians: A community study from urban Eastern India. J Cardiovasc Dis Res 2012;3:204-11.
[61] Prabhdeep Kaur et al. The Metabolic Syndrome and Associated Risk Factors in an Urban Industrial Male Population in South India JAPI 2010; 6:58.
[62] Peppard PE, Young T, Palta M, Skaturd J. Prospective study of the association between sleep-disordered breathing and hypertension. N Eng J Med 2000; 342 : 1378-84.
[63] Wolk R, Shamsuzzaman AS, Somers VK. Obesity, sleep apnea, and hypertension. Hypertension 2003; 42 : 1067-74.
[64] Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165 : 670-6.
[65] Punjabi N, Sorkin J, Katzel L, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002; 165 : 677-82.
[66] Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 2004; 25 : 735-41.

[67] Lam JC, Lam B, Lam CL, Fong D, Wang JK, Tse HF, et al. Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. Respir Med 2006; 100 : 980-7.
[68] Sharma SK, Reddy EV, Sharma A, Kadhiravan T, Mishra HK, Sreenivas V, et al. Prevalence and risk factors of syndrome Z in urban Indians. Sleep Med 2010; 11 : 562-8.
[69] Stoohs RA, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. Am J Respir Crit Care Med 1996; 154 : 170-4.
[70] Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 2006; 5 : 22.
[71] Sharma SK, Kumpawat S, Goel A, Banga A, Ramkrishnan L, Chaturvedi P. Obesity and not obstructive sleep apnea is responsible for metabolic abnormalities in a cohort with sleep disordered breathing. Sleep Med 2007; 8 : 12-7.
[72] Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, et al.: Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond) 2011, 35:971-981.
[73] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al.: Diagnosis and management of the metabolic syndrome: an american heart association/national heart, lung, and blood institute scientific statement. Circulation 2005, 112:2735-2752.
[74] Eckel RH, Alberti KG, Grundy SM, Zimmet PZ: The metabolic syndrome. Lancet 2010, 375:181-183.
[75] Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al.: Identification and characterization of metabolically benign obesity in humans. Arch Intern Med 2008, 168:1609-1616.
[76] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al.: The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008, 168:1617-1624.
[77] Velho S, Paccaud F, Waeber G, Vollenweider P, Marques-Vidal P: Metabolically healthy obesity: different prevalences using different criteria. Eur J Clin Nutr 2010, 64:1043-1051.
[78] Kantartzis K, Machann J, Schick F, Rittig K, Machicao F, Fritsche A, et al.: Effects of a lifestyle intervention in metabolically benign and malign obesity. Diabetologia 2011, 54:864-868.
[79] Pajunen P, Kotronen A, Korpi-Hyovalti E, Keinanen-Kiukaanniemi S, Oksa H, Niskanen L, et al.: Metabolically healthy and unhealthy obesity phenotypes in the general population: the FIN-D2D Survey. BMC Public Health 2011, 11:754.
[80] Geetha L, Deepa M, Anjana RM, Mohan V: Prevalence and clinical profile of metabolic obesity and phenotypic obesity in Asian Indians. J Diabetes Sci Technol 2011, 5:439-446.
[81] Denis GV, Obin MS: 'Metabolically healthy obesity': origins and implications. Mol Aspects Med 2013, 34:59-70.
[82] Pataky Z, Bobbioni-Harsch E, Golay A: Open questions about metabolically normal obesity. Int J Obes (Lond) 2010, 34(Suppl 2):S18-S23.

[83] Anderson PJ, Critchley JAJH, Chan JCN et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. International Journal of Obesity 2001;25:1782.
[84] Lann D, LeRoith D. Insulin resistance as the underlying cause for the metabolic syndrome. Med Clin North Am. 2007; 91 (6):1063-77.
[85] Handelsman Y. Metabolic syndrome pathophysiology and clinical presentation. Toxicologic Pathology. 2009; 37(1):18-20.
[86] Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53(8):2087-94.
[87] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112:2735–2752.
[88] Alberti KGMM, Zimmet PZ. Should we dump the metabolic syndrome? No. BMZ. 2008; 22;336 (7645) : 641
[89] Eckel R, Grundy S, Zimmet. The metabolic syndrome. The Lancet, 2005; 365, 1415-1428.
[90] Wang H, Zhang H, Jia Y, Zhang Z, Craig R, Wang X, et al. Adiponectin receptor 1 gene (ADIPOR1) as a candidate for Type 2 diabetes and insulin resistance. Diabetes, 2004; 53(8), 2132-2136.
[91] Gill H, Mugo M, Whaley-Connell A, Stump C, Sowers J. The key role of insulin resistance in the cardiometabolic syndrome. The Am J Med Sci. 2005; 330(6), 290-294.
[92] Salmenniemi U, Ruotsalainen E, Pihlajamaki J, Vauhkonen I, Kainulainen, S, Punnonen K et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation, 2004; 110, 3842-3848.
[93] Grundy S, Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 2004; 89(6), 2595-2600.
[94] Reilly M, Wolfe M, Rhodes R, Girman C, Mehta N, Rader D. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. Circulation, 2004; 110(7), 803-809.
[95] Gary TC. Metabolic Syndrome or Central obesity Syndrome. Diabetes Care. 2006; vol. 29 no. 3: 752.
[96] Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care, 2005; 28: 1769–1778.
[97] Wingard D, Von Muhlen D, Barrett-Connor E, Kritz- Silverstein D. Factor analysis of proposed components of the insulin resistance syndrome. Diabetes, 1996; 45: 137A.
[98] Hu G, Qiao Q, Tuomilehto J et al. Plasma insulin and cardiovascular mortality in non-diabetic European men and women:a meta-analysis of data from eleven prospective studies. The DECODE Insulin Study Group. Diabetologia 2004;47:1245–56.
[99] Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782-7.

[100] Carey VJ, Walters EE, Colditz GA et al. Body fat distribution and risk of noninsulin-dependent diabetes in women:the Nurses' Health Study. Am J Epidemiol 1997;145:614-19.
[101] Tchkonia T, Corkey BE, Kirkland JL. Current views of the fat cell as an endocrine cell: lipotoxicity.Endocrine Update 2003;26:105-18.
[102] Lee IM, Manson JE, Hennekens CH et al. Body weight and mortality. A 27-year follow-up of middle-aged men. JAMA 1993;270:2823-8.
[103] Pouliot MC, Després JP, Lemieux S et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460-8
[104] Ohlson LO, Larsson B, Svardsudd K et al. The infl uence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985;34:1055-8
[105] Rexrode KM, Carey VJ, Hennekens CH et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998;280: 1843-8.
[106] Parikh RM, Joshi SR, Menon PS, Shah NS. —Index of central obesity – A novel parameter . Medical Hypotheses. 2007: 68(6):1271-5.
[107] Ferranini E, Natali A. Essential hypertension, metabolic disorders and insulin resistance. Am heart J, 1991; Apr; 121(4 Pt 2):1274-82.
[108] Morse S, Zhang R, Thakur V, Reisin E. Hypertension and the metabolic syndrome. Am J Med Sci 2005; 330(6), 303- 310.
[109] Malhotra A, Kang BP, Cheung S, et al. Angiotensin II promotes glucose-induced activation of cardiac protein kinase C isozymes and phosphorylation of troponin I. Diabetes 2001; 50: 1918–1926.
[110] Prasad A, Quyyumi A. Renin-angiotensin system and angiotensin receptor blockers in the metabolic syndrome. Circulation 2004, 110(11), 1507-1512.
[111] Landsberg L. Insulin-mediated sympathetic stimulation:role in the pathogenesis of obesity-related hypertension (or how insulin affects blood pressure and why). J Hyperttens. 2001;Mar; 19(3Pt 2):523-8.
[112] Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simavastatin and niacin, antioxidant vitamins or the combination for the prevention of coronary disease. N Engl J Med 2001; 345:1583- 1592.
[113] Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, et al. Small, dense low-densitylipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. Circulation 1997; 95:69–75.
[114] Sniderman AD, St-Pierre AC, Cantin B, Dagenais GR, Despres JP, Lamarche B Concordance /discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk. Am J Cardiol, 2003; 91:1173–1177.
[115] Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. Creactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol,1999;19:972–978.
[116] Shemesh T, Rowley KG, Jenkins A, Brimblecombe J, Best JD, O'Dea K. Differential association of Creactive protein with adiposity in men and women in an Aboriginal

community in northeast Arnhem Land of Australia. International Journal of Obesity, 2007; 31(1):103– 108.
[117] Mortensen OH, Nielsen AR, Erikstrup C, et al. Calprotectin—a novel marker of obesity. PLoSONE ,2009; 4(10, article e7419).
[118] Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes and inflammation. Circulation. 2005; 111(11), 1448-1454.
[119] Aso Y, Wakabayashi S, Yammoto R, Matsutomo R, Takebayashi, K. and Inukai T. Metabolic Syndrome accompanied by hypercholesterolemia is strongly associated with pro-inflammatory state and impairment of fibrinolysis in patients with type 2 diabetes. Diabetes Care. 2005; 28(9), 2211-2216.
[120] Kraja AT, Province MA, Arnett D, Wagenknecht L, Tang W, Hopkins PN, et al. Do inflammation and procoagulation biomarkers contribute to the metabolic syndrome cluster? Nutr Metabol (Lond), 2007 ;Dec 21; 4:28.
[121] Speakman JR. Thrifty genes for obesity and the metabolic syndrome − time to call off the search? Diabetes and Vascular Disease Research, 2006; 3: 7.
[122] Groop L, Genetics of metabolic syndrome and cardiovascular disease. J Clin Endocrinol Metab. 2006; 89(6), 2595-2600.
[123] Bengtsson K, et al. Polymorphism in the beta (1)- adrenergic receptor gene and hypertension. Circulation, 2001;104, 187-90.
[124] Dionne IJ, et al. Association between obesity and a polymorphism in the beta (1)-adrenoceptor gene (Gly389Arg ADRBI) in Caucasian women . Int J Obes Relat Metab Disord, 2002; 26, 633-9.
[125] Chrousos GP, Gold PW: The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992, 267:1244-1252
[126] Charmandari E, Tsigos C, Chrousos G: Endocrinology of the stress response. Annu Rev Physiol 2005, 67:259-284.
[127] Chrousos GP, Kino T: Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. Ann N Y Acad Sci 2009, 1179:153-166.
[128] Chrousos GP: Stress and disorders of the stress system. Nat Rev Endocrinol 2009, 5:374-381.
[129] Song Q, Wang SS, Zafari M, Genetics of metabolic syndrome. Hospital Physician 2006; 51-61.
[130] Shmulewitz D, et al. Linkage analysis of quantitative traits for obesity, diabetes, hypertension, and dyslipidemia on the island of Kosrae, Federated States of Micronesia. Proc Natl Acad Sci U S A; 2006; 103, 3502-9.
[131] Nader N, Chrousos GP, Kino T: Interactions of the circadian CLOCK system and the HPA axis. Trends Endocrinol Metab 2010, 21:277-286.
[132] Eva Kassi, Panagiota Pervanidou, Gregory Kaltsas, George Chrousos. Metabolic syndrome: definitions and Controversies, Kassi et al. BMC Medicine 2011, 9:48
[133] Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL Jr, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761–88;

[134] National Institutes of Health. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at www.nhlbi.nih.gov/guidelines/cholesterol/index. htm. Accessed June 5, 2009.
[135] "Risk Scoring Systems". http://www.framinghamheartstudy.org/. Retrieved 7 May 2013.
[136] Christina L. Aquilante, Joseph P. Vande Griend, Metabolic syndrome Reviewed by Tracey H. Taveira, Judy W.M. Cheng, David Parra. Available at https://www.accp.com/docs/bookstore/psap/p6b11sample03.pdf
[137] Lindström J, Louheranta A, Mannelin M. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003;26:3230-6.
[138] Tuomilehto J, Lindström J, Eriksson JG et al. Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. NEJM 2001;344:1343-50.
[139] Lorente-Cebrián S, Costa AG, Navas-Carretero S, Zabala M, Martínez JA, Moreno-Aliaga MJ: Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. J Physiol Biochem. 2013Sep; 69(3):633-51.
[140] Kastorini et al. Mediterranean Diet and Metabolic Syndrome JACC Vol. 57, No. 11, 2011; March 15, 2011:1299–313.
[141] M Gharipour, R Kelishadi, N Toghianifar, AA Tavassoli, AR Khosravi, F Sajadi, N Sarrafzadegan, Socioeconomic Disparities and Smoking Habits in Metabolic Syndrome: Evidence from Isfahan Healthy Heart Program, Iran Red Crescent Med J 2011; 13(8):537-543.
[142] Weksler-Zangen, Sarah; Mizrahi, Tal; Raz, Itamar; Mirsky, Nitsa. "Glucose tolerance factor extracted from yeast: oral insulin-mimetic and insulin-potentiating agent: in vivo and in vitro studies". British Journal of Nutrition 2012; 9:108 (5): 875–882. doi:10.1017/S0007114511006167. PMID 22172158.
[143] Geiger H, Wanner C (2012). "Magnesium in disease". Clin Kidney J 5 (Suppl 1): i25–i38. doi:10.1093/ndtplus/sfr165
[144] Bhansali et al: G. Sylvestre in Metabolic Syndrome. Indian J Med Res 137, June 2013; 1174-1179.
[145] Capasso et al.: Combination of inositol and alpha lipoic acid in metabolic syndrome-affected women: a randomized placebo-controlled trial. Trials 2013 14:273.
[146] E. Tsiani, I.G. Fantus: Vanadium Compounds Biological Actions and Potential as Pharmacological Agents Trends Endocrinol Metab 1997;8:51–58.
[147] Zempleni et al.: Biotin and biotinidase deficiency. Expert Rev Endocrinol Metab. 2008 November 1; 3(6): 715–724. doi:10.1586/17446651.3.6.715.
[148] Lahbib A, Ghodbane S, Sakly M, Abdelmelek H.Vitamins and glucose metabolism: The role of static magnetic fields. Int J Radiat Biol. 2014 Aug 4:1-6. PMID: 24899393.
[149] Baby Joseph and D Jini Antidiabetic effects of Momordica charantia (bitter melon) and its medicinal potency Asian Pac J Trop Dis 2013; 3(2): 93-102.
[150] Padiya et al. Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats Nutrition & Metabolism 2011, 8:53.

[151] DG Arbeláez et al. Aged garlic extract improves adiponectin levels in subjects with metabolic syndrome: a double-blind, placebo-controlled, randomized, crossover study. Mediators Inflamm. 2013:285795. doi: 10.1155/2013/285795.
[152] Ramadan G et al. Anti-metabolic syndrome and immune-stimulant activities of Egyptian fenugreek seeds in diabetic/obese and immunosuppressive rat models. Br J Nutr. 2011 Apr;105(7):995-1004. doi: 10.1017/S0007114510004708. Epub 2010 Dec 23.
[153] S Kannappan, CV Anuradha, Insulin sensitizing actions of fenugreek seed polyphenols, quercetin & metformin in a rat model Indian J Med Res 2009; Apr:129: 401-408.
[154] Robins SJ, Rubins HB, Faas FH et al. Insulin resistance and cardiovascular events with low HDL cholesterol. The Veterans Affairs HDL Intervention Trial (VA-HIT). Diabetes Care 2003;26(5):1513-7.
[155] Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16
[156] Haffner SM, Alexander CM, Cook TJ et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes mellitus or impaired fasting glucose levels: subgroup analysis on the Scandinavian Simvastatin Survival Study. Arch Intern Med 1999;159(22):2661-7
[157] Goldberg RB, Mellies MJ, Sacks FM et al. for the CARE investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. Circulation 1998;98:2513-9.
[158] Chobanian AV, Bakris GL, Black HRet al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee The Jnc 7 Report JAMA. 2003 May 21;289(19):2560-72. Epub 2003 May 14
[159] Laragh JH, Baer L, Brunner HR, Buhler FR, Sealey JE, Vaughan ED, Jr. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Am J Med 1972;52:633–652.
[160] Stanton AV, Dicker P, O'Brien ET. Aliskiren monotherapy results in the greatest and the least blood pressure lowering in patients with high- and low-baseline PRA levels, respectively. Am J Hypertens 2009;22:954–957.
[161] Mancia G, De Backer G, Dominiczak A, et al.; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25:1105–1187
[162] Mancia G, Bombelli M, Corrao G, et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension 2007;49:40–47.
[163] Nelson M. Drug treatment of elevated blood pressure. Aust Prescr 2010;33:108–12.
[164] Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. NEJM 2002;346(6):393-403.

[165] Buchanan TA, Xiang AH, Peters RK et al. Preservation of pancreatic beta cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796-803.
[166] Durbin RJ. Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. Diabetes, Obesity and Metabolism 2004;6:280-5.
[167] Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. Apr 19 2005;142(8):611-9.
[168] Nieuwdorp M, Stroes ES, Kastelein JJ. Normalization of metabolic syndrome using fenofibrate, metformin or their combination. *Diabetes Obes Metab*. Nov 2007;9(6):869-78.
[169] Derosa G, D'Angelo A, Ragonesi PD, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with metformin. *Intern Med J*. Feb 2007;37(2):79-86.
[170] Bragt MC, Popeijus HE. Peroxisome proliferator-activated receptors and the metabolic syndrome. *Physiol Behav*. May 23 2008;94(2):187-97.
[171] Chiasson JL, Josse RG, Gomis R et al. STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003 Jul 23;290(4):486-94.
[172] Torgerson JS, Hauptman J, Boldrin MN et al. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155-61.
[173] Kini S, Herron DM, Yanagisawa RT. Bariatric surgery for morbid obesity--a cure for metabolic syndrome?.*Med Clin North Am*. Nov 2007;91(6):1255-71, xi.
[174] Williams S, Cunningham E, Pories WJ. Surgical treatment of metabolic syndrome.Med Princ Pract. 2012;21(4):301-9. doi: 10.1159/000334480. Epub 2012 Jan 4.
[175] Bagry HS, Raghavendran S, Carli F. Metabolic syndrome and insulin resistance: perioperative considerations. *Anesthesiology*. Mar 2008;108(3):506-23.