

**Factors contributing in incidence and diagnosis of metabolic syndrome:
Updated Mini review**

Abstract

It has been well-established that obesity is the major contributing factor for the development of metabolic syndrome (MetS), diabetes, cardiovascular disease and certain types of cancer. According to WHO, 44% increase of diabetes, 23% increase of ischaemic heart disease, and between 7% and 41% increase of certain cancer are due to obesity. The Middle East region is reported to have the highest prevalence of diabetes in adults in the world. In Saudi Arabia, over 35% of the population are obese, and it is estimated that 24% of adult has diabetes including undiagnosed diabetes cases. Obesity and chronic metabolic disease associated obesity impose the heavy financial burden on national healthcare in the Gulf countries as they do in most countries worldwide. Plasminogen Activator Inhibitor-1 (PAI-1) is the primary of four serine peptidase inhibitors that functions to modulate extracellular matrix remodeling and fibrinolysis. The link between PAI-1 and MetS has been established. This review screening the association between PAI-1, trace elements, vitamin D, obesity hormone and expression of obesity genes for early prediction of MetS for control and management to prevent late complications.

Keywords: Metabolic syndrome-insulin-plasminogen factor-trace elements

Background

In Gulf countries, it was reported that non-communicable diseases (NCDs) as obesity will cost \$68 billion in 2030. The medical healthcare expenditures that are increased ten times higher (\$3,686 vs. \$380) [1]. These reports underline the urgent needs for a strategy to reduce the occurrence of these diseases and health care burden derived from it not only in the Middle East but also globally [2]. The obesity rate has increased dramatically worldwide and emerged as a major global challenge. Obesity is a serious health concern because it is a risk factor for other diseases including diabetes, coronary heart disease, hypertension and certain types of cancer. In the Middle East, the prevalence of obesity has arisen as a substantial issue with 35% of obese rate in adult, and in accordance, the highest diabetes rate in the world [3]. A recent report has shown that 35.2% of Saudi Arabian population is obese, the second highest in the world. Current therapeutic approaches to treat obesity using drugs are unsatisfactory due to numerous side effects [4].

Diet-induced metabolic syndromes are widely spread nutritional disorders around the world and have arisen as a growing global challenge. Among them, obesity is a

42 significant risk factor for other diseases including diabetes, coronary heart disease,
43 hypertension, atherosclerosis and certain forms of cancer. Obesity is defined by a body
44 mass index ≥ 30 according to the World Health Organization (WHO) [5]. Obesity arises
45 from energy imbalance due to excessive energy intake from food consumption and
46 insufficient energy expenditure which includes basal metabolism, physical activity and
47 adaptive thermogenesis. In the Middle East, the prevalence of obesity has increased
48 dramatically and become a serious health concern in the recent decades [6]. There is a
49 notable increase in the incidence of obesity in Arabic-speaking countries with a
50 prevalence of 2 to 55% in females and 1 to 30% in males. Increased consumption of fats,
51 sugars, and carbohydrates in these countries is associated with change of dietary habits by
52 Westernization, which can increase the risk for obesity. It is now known that obesity is
53 the major cause of metabolic diseases such as type 2 diabetes and cardiovascular diseases
54 (CVDs), yet mechanistic understanding of this pathology and current therapeutics are
55 unsatisfactory [7].

56 The identification of genes that increase incidence for development of obesity
57 has become interesting. One of these genes is the GNB. Its name derived from the G-
58 protein (GNB3) gene, which formed from 12 exons, present on chromosome 12p13 and
59 produce $\beta 3$ unit of G proteins. The polymorphism of this gene leads to a truncated splice
60 variant. The *GNB3* 825T allele product has been associated with obesity, hypertension,
61 and atherosclerosis [8].

62

63 The burgeoning rate of obesity is not only indicated in adult population, but also in
64 children and adolescents [9]. This high prevalence of obesity has paralleled the rise of
65 diabetes and hypertension. Poor eating habits and physical inactivity due to their greasy
66 and high calorie diet and sedentary lifestyle, respectively, are known to be the major
67 contributors of obesity in the Middle Eastern population. The changes in diet of the Arab
68 World includes increased calorie intake and substitution of the traditional diet with
69 refined and processed foods and diets high in fat and salt. Recent studies have reported
70 that natural compounds found in cruciferous vegetables such as broccoli, cabbage and
71 radish have numerous beneficial effects on various diseases such as cancer,
72 cardiovascular disease, and inflammation [10]. Adipogenesis and lipogenesis through cell
73 cycle arrest and activation of AMP-activated protein kinase (AMPK) [11], but also
74 promoting lipolysis mediated by activation of hormone-sensitive lipase (HSL), a lipase in
75 adipocyte. Moreover, the exact mechanism of action of them in various organs which are
76 closely related to obesity and insulin resistance have not been clearly understood.
77 Therefore, it is important to prevent overweight or obesity to reduce the risk factor
78 threatening our healthy lives. Regardless of which criteria are used, the primary concern
79 is early detection of potential CVD complications and early intervention [12]. The
80 prevalence of MetS in Saudi subjects was reported by Al-Nozha et al. to be 39.3% [13].
81 The aim of current survey for monitoring major factors that contribute for metabolic
82 syndrome like plasma vitamin B₁₂, trace elements, prothrombic factors (PAI-1), lipid
83 profile, hormonal changes (insulin, leptin and Ghrelin) as a predictive biomarkers for
84 metabolic syndrome.

85 **Prevalence of MetS estimates by coagulation factors**

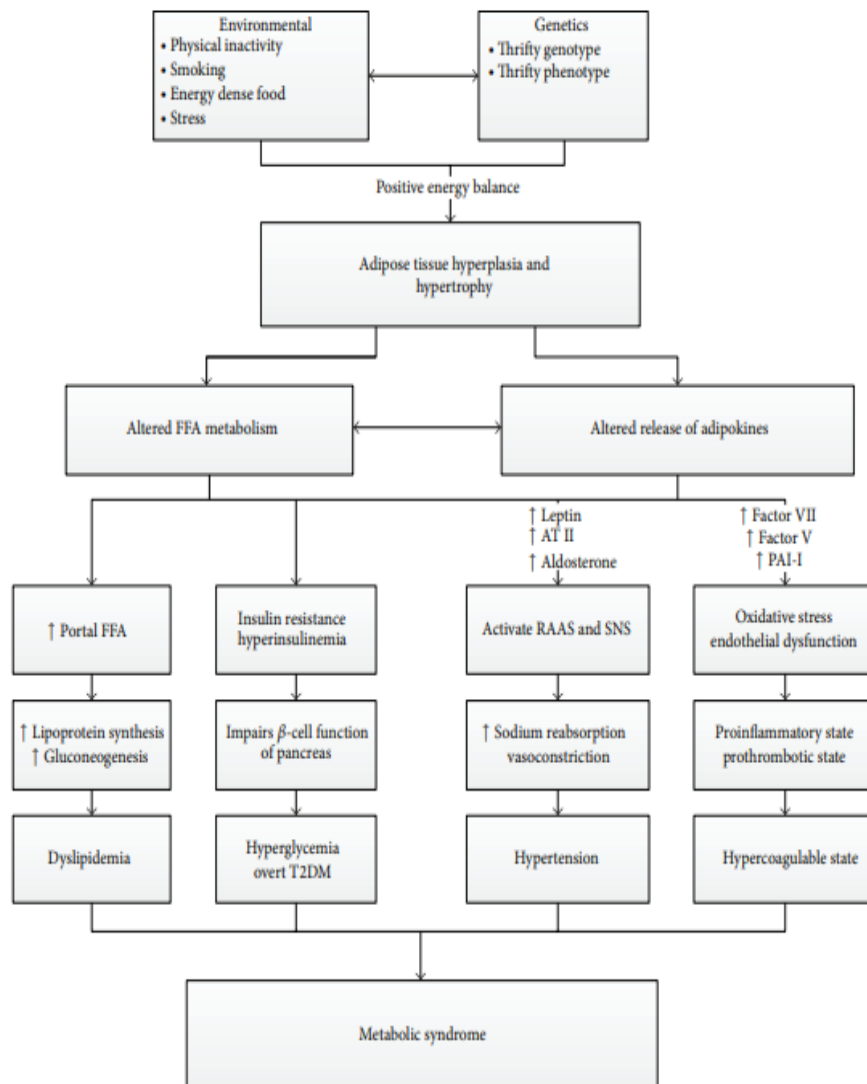
86 Plasminogen Activator Inhibitor-1 (PAI-1) is a serine protease inhibitor that play a role in
87 modulation of fibrinolysis. Its level is regarded as a index of an abnormal fibrinolysis
88 and thrombosis. The correlation between PAI-1 and MetS was reported to be elevated
89 and strongly association such MetS [14-17]. In efforts to treat obesity and its related
90 metabolic diseases, numerous synthetic drugs and therapeutic approaches have been
91 develop [18]. However, currently there are no effective drugs for obesity without side
92 effects [19]. For examples, several drugs such as sibutramine andreductil are withdrawn
93 from the pharmaceutical market due to their severe side effects [13]. Moreover, even
94 though many synthetic drugs undergo developmental process, they failed during clinical
95 phase trials due to their ineffectiveness or side effects.

96 **Prevalence of MetS estimates by age**

97 The risk of MetS is correlated to age, It was found that, less than 10% of subjects at
98 age 20s and 40 % at age 60s were affected. On the other hand, other reports revealed that
99 in school children other factors may contribute as fast foods and soft drinks. There was
100 correlation between childhood MetS and adult incidence of CHD [20]. It has been
101 suggested that SES influences nutrition and sedentary habits, which are highly related to
102 MetS components. Lower levels of education are associated with higher prevalence of
103 MetS [21].

104

105



106

107

108

109 Figure (1): Factors associated with MetS. (FFA: free fatty acid, ATII: angiotensin
 110 II, PAI-1: plasminogen activator inhibitor-1, RAAS: renin angiotensin aldosterone
 system, SNS: sympathetic nervous system [21].

111

Prevalence of MetS estimates by oxidative stress

112

Another factor contributing to the development of the MetS is excessive ROS formation

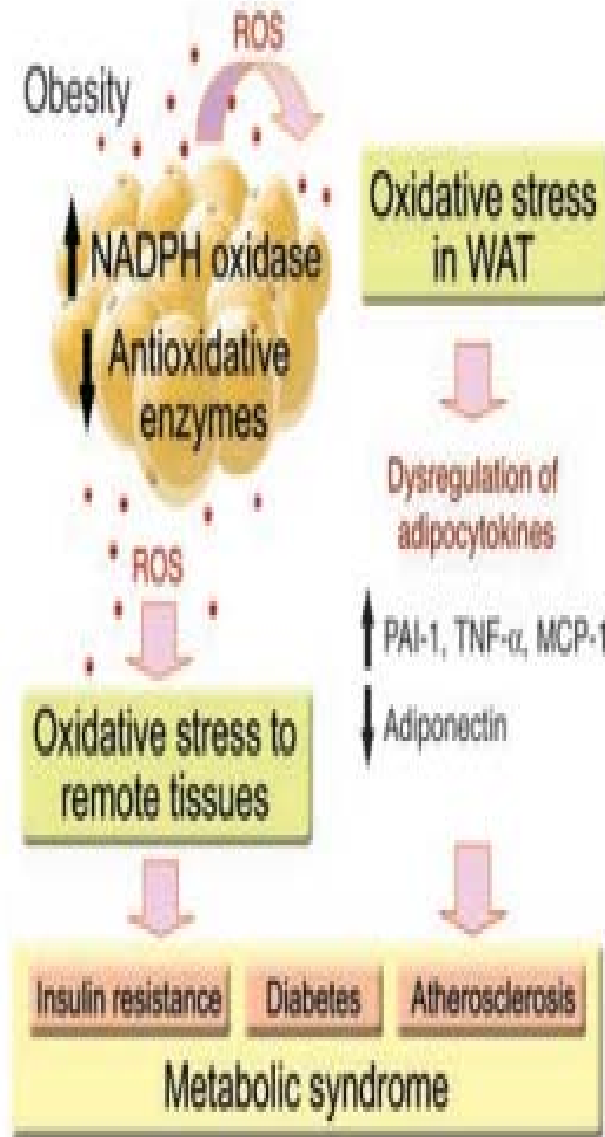
113

which can alter the mitochondrial function and endoplasmic reticulum which again will

114

lead to defective insulin secretion and DM2. Increased oxidative stress in accumulated

115 fat, via increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and
116 decreased antioxidant enzymes [15].



117

118 Figure (2): Impact of ROS production in accumulated fat contributes to
119 metabolic syndrome [15].

120

121

122

123

124 **Prevalence of MetS estimates by insulin action**

125 Insulin resistance with hyperinsulinemia seems to be a central factor in the pathogenesis
126 of the MetS. An insulin-resistant state interferes with the hormonal actions taking place in
127 the liver. Insulin produced in the β -cells of the pancreas travels quickly to the liver via the
128 portal vein, and in the presence of the MetS, insulin has a selective dysfunction so that it
129 does not diminish the hepatic glucose output, but rather increases it, and still, like in the
130 normal state, increases the de novo lipogenesis, thereby releasing triglycerides to the
131 circulation, causing dyslipidemia [22]. Further, insulin resistance causes increased renal
132 sodium reabsorption and stimulate the sympathetic nervous system which can result in
133 hypertension [23].

134 **Prevalence of MetS estimates by trace elements**

135 Trace elements has an important role in metabolism, growth, immunological,
136 and neurological functions Copper (Cu), one of these elements, is mainly found in
137 shellfish, organ meats, nuts, seeds, vegetables, and grains [24]. Throughout the years it
138 has been shown that Cu abnormalities are linked to CVD [25] and cancer [20]. In fact, its
139 deficiency may lead to arterial diseases and myocardial disease, besides pigmentation
140 loss and neurological effects. Cu has an important role in the defense against free radical
141 damage as an antioxidant [26]. Previous study found that Cu levels were significantly
142 higher in subjects with MetS than in subjects without MetS, however, they did not
143 analyze these values according to weight, since they also found that serum Cu levels were
144 significantly higher in obese than in normal subjects and it is known that increasing
145 weight increases the risk for developing MetS. The causal relationship between obesity
146 and concentration of iron in the teenagers was already established [27]. Further to that, a
147 causal association between low blood Fe concentrations and adiposity in people has been
148 noted [28].

149 **References**

- 150 1. Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-
151 causes: findings from the National Health and Nutrition Examination Survey II Mortality
152 Study. *Atherosclerosis*. 2004; 173: 309-14.
- 153 2. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic
154 syndrome in the United States, 2003-2012. *Jama*. 2015; 313: 1973-4.
- 155 3. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al.
156 Diagnosis and management of the metabolic syndrome: an American Heart
157 Association/National Heart, Lung, and Blood Institute scientific statement. *Current
158 opinion in cardiology*. 2006; 21: 1-6.
- 159 4. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A
160 Consensus Statement from the International Diabetes Federation. *Diabetic medicine : a
161 journal of the British Diabetic Association*. 2006; 23: 469-80.

- 162 5. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C, American Heart A,
163 et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood
164 Institute/American Heart Association conference on scientific issues related to definition.
165 *Circulation*. 2004; 109: 433-8.
- 166 6. Bhandari R, Kelley GA, Hartley TA, Rockett IR. Metabolic syndrome is associated
167 with increased breast cancer risk: a systematic review with meta- analysis. *International*
168 *journal of breast cancer*. 2014; 2014: 189384.
- 169 7. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al.
170 Adiponectin as a biomarker of the metabolic syndrome. *Circulation journal : official*
171 *journal of the Japanese Circulation Society*. 2004; 68: 975-81.
- 172 8. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic
173 syndrome. *Annals of the New York Academy of Sciences*. 2010; 1212: E1-E19.
- 174 9. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al.
175 Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal*
176 *of clinical investigation*. 2004; 114: 1752-61.
- 177 10. Raghavan S, Subramaniyam G, Shanmugam N. Proinflammatory effects of
178 malondialdehyde in lymphocytes. *Journal of leukocyte biology*. 2012; 92: 1055-67.
- 179 11. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-
180 Gonzalez A, Esquivel-Chirino C, et al. Inflammation, oxidative stress, and obesity.
181 *International journal of molecular sciences*. 2011; 12: 3117-32.
- 182 12. Mayeux R. Biomarkers: potential uses and limitations. *NeuroRx : the journal of the*
183 *American Society for Experimental NeuroTherapeutics*. 2004; 1: 182-8.
- 184 13. Global Strategy on Diet, Physical Activity and Health. Geneva, World Health
185 Organization, 2004. Available in six languages at:
186 <http://www.who.int/dietphysicalactivity/strategy/eb11344/en/index.html> [accessed 30
187 November 2011].
- 188 14. WHO global strategy on diet, physical activity and health: a framework to monitor
189 and evaluate implementation. Geneva, World Health Organization, 2008.
- 190 15. Sacks G, Swinburn B, Lawrence M. Obesity Policy Action framework and analysis
191 grids for a comprehensive policy approach to reducing obesity. *Obesity Reviews*,
192 2008,10(1):76–86.
- 193 Population-based prevention strategies for childhood obesity: report of a WHO forum
194 and technical meeting, Geneva, 15–17 December 2009. Geneva, World Health
195 Organization, 2010.
- 196 16. Carter R et al. Priority setting in health: origins, description, and application of the
197 Australian ‘Assessing Cost-Effectiveness’ (ACE) initiative. *Expert Review of*
198 *Pharmacoeconomics & Outcomes Research*, 2008, 8(6):593–617.
- 199 17. Haby MM et al. A new approach to assessing the health benefit from obesity
200 interventions in children and adolescents: the assessing cost-effectiveness in obesity
201 project. *International Journal of Obesity (London)*, 2006, 30(10):1463–75.
- 202 18. Carter R et al. Assessing Cost-Effectiveness in Obesity (ACE-Obesity): an overview
203 of the ACE approach, economic methods and cost results. *BMC Public Health*, 2009,
204 9:419.
- 205 19. Tackling Obesities: Future Choices – Project report. Foresight, London, Government
206 Office for Science, 2007. Available at: [http://www.bis.gov.uk/foresight/our-](http://www.bis.gov.uk/foresight/our-work/projects/published-projects/tackling-obesities)
207 [work/projects/published-projects/tackling-obesities](http://www.bis.gov.uk/foresight/our-work/projects/published-projects/tackling-obesities) [accessed 30 November 2011].

208 20. Robertson A et al., eds. Food and health in Europe: a new basis for action (WHO
209 regional publications. European series, No. 96). Copenhagen, World Health
210 Organization, 2004.65 Best options for promoting healthy weight and preventing weight
211 gain in NSW. Sydney, New South Wales Department of Health, 2005.

212 21. Griffiths J, Maggs H, George E. 'Stakeholder Involvement': Background paper
213 prepared for the WHO/WEF joint event on Preventing Noncommunicable Diseases in the
214 Workplace (Dalian/China, September 2007). Geneva, World Health Organization, 2008.

215 Milio N. Nutrition and health: patterns and policy perspectives in food-rich countries.
216 *Social Science & Medicine*, 1989, 29(3):413–23.

217 22. Swinburn BA. Obesity prevention: the role of policies, laws and
218 regulations. (Commentary). *Australia & New Zealand Health Policy*, 2008, 5:12.

219 23. Snowdon W et al. Prioritizing policy interventions to improve diets? Will it work, can
220 it happen, will it do harm? *Health Promotion International*, 2010, 25(1):123–33.

221 24. Keating CL et al. Cost-effectiveness of surgically induced weight loss for the
222 management of type 2 diabetes: modeled lifetime analysis. *Diabetes Care*, 2009,
223 32(4):567–74.

224 25. Picot J et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss)
225 surgery for obesity: a systematic review and economic evaluation. *Health Technology*
226 *Assessment*, 2009, 13(41):1–190, 215–357, iii-iv.

227