COMPREHENSIVE REVIEW: METABOLIC SYNDROME PREDICTING, PREDIABETES, TYPE-2 DIABETES

Tilson Mathew.S[1], K. Yogananthan. H[1], Yuvan Hadhithya[1], K.I. Akila[1*], K.Karthickeyan*

Abstract

Due to the significant morbidity and death rates associated with diabetes mellitus worldwide, it is crucial to identify risk factors in populations at risk early in the course of illness. The term "metabolic syndrome" refers to a collection of interrelated physiological, biochemical, clinical, and metabolic variables that significantly raises the risk of type 2 diabetes, cardiovascular disease, and all-cause mortality. The chance of developing pre-diabetes and the progression of T2DM over time may be predicted using the MetS severity score. We emphasize the importance of early metabolic syndrome identification in predicting pre-diabetes and T2DM. The accuracy of this as a diagnostic tool is demonstrated by the relationship between the severity of the metabolic syndrome (MetS) and the likelihood of developing type 2 diabetes in the future.

1-Pharm.D V year, Department of Pharmacy Practice, School of Pharmaceutical sciences, Vels Institute of Science, technology and advanced studies, Chennai, Tamil Nadu, India-600117

1*- Pharm.D Post Baccalaureate II year, Department of Pharmacy Practice, School of Pharmaceutical sciences, Vels Institute of Science, technology and advanced studies, Chennai, Tamil Nadu, India-600117

* - Professor and Head, Department of Pharmacy Practice, School of Pharmaceutical sciences, Vels Institute of Science, technology and advanced studies, Chennai, Tamil Nadu, India-600117

*-Corresponding author: Dr. K.Karthickeyan M. Pharm, MBA, PGDCR, PhD., Professor and Head, Department of Pharmacy Practice,

School of Pharmaceutical sciences,

Vels Institute of Science, technology and advanced studies,

PV Vaithyalingam road, Pallavaram,Chennai, Tamil Nadu, India-600117

E-mail ID: hodppractice@velsuniv.ac.in

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4782

INTRODUCTION

A person with metabolic syndrome is known to have a dysfunctional metabolic mechanism that puts them at risk for comorbidities. Cardio metabolic conditions exacerbate and encourage them. For instance, diabetes and insulin resistance can both be brought on by main weight issues, hyperlipidemia, and high blood pressure. High blood pressure also increases the risk of developing diabetes. The majority of the time, people experience multiple types of this issue concurrently. Prediabetes is diagnosed using the same lab tests for blood sugar monitoring that are used to diagnose diabetes. The person's blood sugar levels will show a higher BG than the typical range but below full diabetes, which is between 125mg/dL. The development of type 2 diabetes is significantly increased by prediabetes, 25% of people with 3 to 5 years of experience with Pre-DM will acquire type 2 diabetes mellitus (T2D). [1] The global epidemic of type 2 diabetes is worsening. According to the American Diabetes Association, between 33.0% and 49.0% of diabetes is a result of patients failing to achieve the goals of glucose control, blood pressure, and cholesterol. The failure to control glucose adds to the high numbers associated with the severity of the condition. There is a direct correlation between HbA1c, fasting insulin, insulin resistance, and metabolic syndrome severity (MetS). Hence, the MetS severity score (also known as the MestS Z-score) can be used to predict the future risk of developing hyperglycemia and T2DM. The prevalence of type 2 diabetes is a worry for world health [2].

HISTORY

The word "metabolic syndrome" wasn't first used until the 1950s, when it then became widely used. Herman Haller, who was researching the dangers of atherosclerosis, coined the phrase "metabolic syndrome" in 1977. He coined the word to highlight the links between fatty liver disease (hepatic steatosis), obesity, diabetes mellitus, high blood lipids, and a high uric acid level (predisposes to gout) and the increased likelihood of getting atherosclerosis. [3]. Gerald Reaven put forth the "syndrome X" theory in 1988, speculating that insulin resistance might be what connects this collection of anomalies.

The history of the word "pre-diabetes" has been rocky. The World Health Organization (WHO) [4] abandoned the term in 1980, primarily because many people with borderline glucose levels do not develop diabetes and because many people would be needlessly alarmed. These issues still exist. To encompass impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), but not other diabetes risk factors, the American Diabetes Association (ADA) reintroduced pre-diabetes in 2005 [5]. The term was once more rejected and discouraged from the use by WHO's diabetes task group in 2008 [5,2]. They recommended "intermediate hyperglycemia" as an alternative word to denote IGT and IFG. The ADA still refers to pre-diabetes as having IFT, IGT, and now having an HbA1c of 5.7% to 6.4% [5,3].

When your body's cells reject insulin's intended result of pushing blood glucose into the cells' interiors, type 2 diabetes develops. Insulin resistance is the medical term for this issue. Blood glucose levels start to increase as a result. Diabetes type 2 is a chronic disease. Elevated blood sugar levels are a sign of it[6]. Any classification of pre-diabetes that excludes IGT and/or IFG leaves out additional diabetes risk factors like metabolic syndrome or a family history of type 2 diabetes. The fact that many people with either IFG or IGT will not develop type 2 diabetes is another telling argument against the label pre-diabetes. Another name might be more appropriate for this purpose. The term "intermediate hyperglycemia" proposed by the WHO task group has not yet gained much traction [7].

The pancreas "perceives" growing blood glucose levels in persons with insulin

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4783

resistance. To maintain consistent blood sugar levels, the pancreas generates additional insulin. With time, the body's insulin intolerance worsens. The pancreas produces increasingly more insulin in reaction. The pancreatic eventually becomes "exhausted". It is unable to meet the demand for ever-increasing amounts of insulin. It passes to waste. Blood glucose levels consequently start to increase. Diabetes risk is significantly increased by obesity[9].

EPIDEMOLOGY

The incidence of metabolic syndrome frequently accompanies that of obesity and type 2 diabetes (one of the outcomes of MetS). Between 1988–2010, the average BMI in the United States climbed by 0.37 percent per year in both men and women, while the average waist circumference increased by 0.37 and 0.2 percent per year in women. According to 2017 CDC data, over 30,2 million adults aged 18 or older, or 12.2% of U.S. adults, have type 2 diabetes (T2DM). One-fourth of these individuals (23.8%) were unaware that they had diabetes.[10,1]

The prevalence of prediabetes or MetS was approximately thrice higher. Hence, around one-third of American individuals have metabolic syndrome. Some ethnic groups have an even greater incidence of T2DM: 15% among American Indians and 4.3% among Chinese Americans. In South Asian Americans, the prevalence of meta Based on WHO standards, the prevalence of overweight and obesity in China grew from 14.6% to 21.8% between 1992 and 2002. a greater incidence of metabolic syndrome and abdominal obesity According to the IDF diabetes atlas [8], the prevalence of diabetes worldwide in 2015 was 8.8% (415 million) and is projected to rise to 10.4% (642 million) by 2040. The region with the greatest prevalence of diabetes was North America and the Caribbean (11.5%). More than half of all diabetics resided in Southeast Asia and the Western Pacific. In Africa, the prevalence is still quite low. In the next 25 years, however, sub-Saharan Africa and the Middle East/North Africa are projected to have the highest diabetes growth rates (141 and 104%, respectively).[10,2]

We do not have comparable worldwide data on metabolic syndrome, which is more difficult to assess, but given that MetS is approximately three times more prevalent than diabetes, its global prevalence can be approximated to be approximately 25 percent of the world's population. In other words, metabolic syndrome today affects over a billion people worldwide. Estimates of prevalence vary depending on the criteria used to define MetS.[10,3]

PATHOGENESIS:

MetS is brought on by a complex interaction of environmental as well as genetic variables.. Endocrine regulation of visceral adipose tissue, insulin resistance, and hypertension have been mentioned as pathophysiological factors. In addition, the literature emphasizes the role of endothelial dysfunction, systemic inflammation, and oxidative stress in the etiology of MetS. Due to overlapping alterations, it is difficult to define particular pathophysiological pathways, as one pathology causes the next, which dictates still another, and so on.[11'1]

OBESITY

Visceral obesity is one of the primary agents of transformation. Adipose tissue accumulation contributes to the breakdown of homeostasis and the beginning of adaptive alterations. Increased plasma FFA levels result in ectopic lipid accumulation and lipotoxicity as a consequence of a situation of positive energy balance and low-grade chronic inflammation. It is hypothesized that visceral adipose tissue buildup precedes the development of insulin resistance, and its participation in MetS is connected with the release of several inflammatory mediators. In turn, inflammation is closely connected to the pathophysiology of atherosclerosis,

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4784

creating a relationship between obesity and an elevated risk of CVD . Overall, adipose tissue is an endocrine organ. Many bioactive molecules called adipocytokines are secreted by adipocytes to maintain systemic homeostasis. A deviation in the profile of adipocytokines may drive the development of MetS and play a significant role in cellular dysfunction. Resist in, leptin, adiponectin, TNF-, and IL-6 are the cytokines that most frequently contribute to problems. Resist plays a unique role, as its enhanced secretion by adipocytes in obese people coincides with elevated cellular insulin resistance.[11,2]

INSULIN RESISTANCE:

Insulin resistance is the key component of MetS (IR). Insulin resistance reduces the responsiveness of many organs, such as the liver, skeletal muscle, and adipose tissue, to insulin. Insulin modulates a wide variety of cellular activities by activating two essential post-receptor transduction signaling cascades, PI3K and RAS-MAPK. Insulin's effect on metabolism is caused by the activation of the PI3K cascade, which regulates the activity of transcription factors responsible for cell proliferation and death. This route in vascular endothelium induces vasodilation by increasing nitric oxide production[11,3].

MetS is considered to be caused by an increase in circulating free fatty acids (FFAs) that is mediated by insulin resistance. Insulin resistance contributes to the development of hypertension due to the lack of insulin's vasodilator action and vasoconstriction resulting from FFAs. In addition to enhanced sympathetic activity and sodium reabsorption in the kidneys, there are nine more processes. Insulin resistance also causes an increase in serum viscosity, the development of a prothrombotic state, and the production of pro-inflammatory cytokines from adipose tissue, all of which raise the risk of cardiovascular disease.[10,4]

FREE RADICALS

Free radicals are minute, highly reactive, and diffusible molecules with cytotoxic and genotoxic tendencies.Several instances of defective homeostasis are connected with the formation of reactive oxygen species (ROS), but some of them, known as bioradicals, arise from physiological processes. The abnormal hyper- or hypoactivation of certain cellular signalling pathways causes persistent inflammation and an imbalance in cellular death and proliferation. Visceral obesity leads to the excessive synthesis of adipokines in MetS. Abnormal adipokine levels are associated with a sustained increase in systemic inflammation, and the migration of macrophages into visceral adipose tissue has been suggested as a potential component boosting the generation of reactive oxygen species. ROS directly contributes to autonomic balance dysregulation and, thus, insufficient blood pressure regulation.[11,1]

CARDIOVASCULAR CONSEQUENCES

Extensive alterations in the cardiovascular system result in cardiomyopathy, microcirculation damage, and impaired endothelial function [9][10]. Each MetS aspect stands alone as a risk factor for cardiovascular diseases. MetS is linked to a higher risk of atherosclerosis, myocardial infarction, and heart failure, according to research. Concentric left ventricular hypertrophy and systolic or diastolic dysfunction are symptoms of obesity-associated cardiomyopathy. In addition, it has been demonstrated that myocardial contractility, systolic velocity, and left ventricular shortening are affected. Changes in microvascular tone and density are caused by an imbalance between oxygen supply and tissue metabolism in diverse vascular beds. Significant differences in the regulation of arteriolar resistance Young First-degreedegree Relative adults have a significant prevalence of MetS, according to Siewert et al. [18]. Preventative interventions at a young age seem pertinent because MetS

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4785

and T2DM are closely related diseases that are brought on by the same metabolic imbalances.are primarily responsible for these variations in MetS. MetS is related with reduced nitric oxide bioavailability and endothelial dysfunction. Increased production of vasoconstrictors, such as endothelin-1 (ET-1), thromboxane A2 (TXA2), and prostaglandin H2, is the underlying process that contributes to endothelial disease (PGH2)[11,2]

METABOLIC SYNDROME'S PREDICTIVE POTENTIAL REGARDING PREDIABETES AND TYPR-2 DIABETES

Rokhsareh Meamar et al. finished the first population-based study to assess the association between MetS Z-score and the occurrence of pre-diabetes/T2DM in the normal FDR population at the first visit. It was revealed that the severity of the MetS score as a linear measure is a predictor for the future incidence of T2DM and prediabetes. This correlation was moderate in the whole population (AUC = 0.63) and slightly stronger in the FDR female population (AUC = 0.68). Prior to this study, the MetS Z-score predicted CVD and diabetes similarly in non-FDR populations.[12]

Future incidence of T2DM in adults may be predicted by the severity of MetS in children, according to DeBoer et al. Several studies have demonstrated a high association between MetS Z-score and HbA1c, fasting insulin, and insulin resistance[14]. These findings imply that the MetS Z-score could be utilized to assess risk and track the evolution of T2DM over time[12,1]. With an odds ratio of 2.7 by the mean age of 38.5, it has been discovered that the MetS Z-score from childhood can predict future risk of diabetes. [12,2].

Due to disagreement about the definition that would be most appropriate or even whether MetS should be classified as a syndrome[13],We discovered comparable outcomes: In the whole FDR population, the risk ratio for each 1.0 unit rise in adulthood MetS Z-score to predict diabetes and pre-diabetes at a mean age of 43 was 2.69 and 1.76, respectively. In addition, the MetS Z-score is correlated with juvenile obesity and is a major risk factor for prediabetes and the development of T2DM [15].

Gurka et al. [16,17] have developed MetS Z-scores that are gender- and race/ethnicity-specific. Siewert et al.[18] demonstrated that the prevalence of MetS is high among young FDR adults. As MetS and T2DM are closely linked diseases and are induced by the same metabolic abnormalities, preventative treatments at a young age seem relevant. The paternal history of T2DM was independently associated with a higher incidence of pre-diabetes/T2D in adolescents in a recent cohort survey performed in Iran [HR = 1.63 (1.02-2.63)]. [19]

According to the research conducted by Watip Tangjittipokin et al., 28.5% of the PreDM individuals had MetS. They were older and had characteristics indicative of increased insulin resistance, including a higher BMI, blood pressure, waist circumference, and triglyceride level, as well as a lower HDL cholesterol level [20].Ghachem's research indicated that various types of Pre-diabetes are connected with distinct MetS characteristics, including BMI, waist circumference, lipid parameters, and CRP level[21]. A multivariate logistic regression analysis with age, BMI, and gender adjustments revealed that males with higher BMI, MetS score, and lower HDL cholesterol levels were independent predictors of PreDM.Obesity was observed to have a substantial effect on the onset of PreDM in the Northeast Chinese population[22].

The relationship between childhood metabolic syndrome and adult metabolic syndrome and type 2 diabetes mellitus (T2DM) 25 to 30 years later was prospectively examined by John A. Morrison et al. [23,24]. Age at follow-up assessment and paediatric metabolic

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4786

syndrome both served as reliable indicators of cardiovascular disease. Pediatric metabolic syndrome and variations in BMI percentiles by age from childhood to adulthood were important indicators of adult metabolic syndrome.. Screening children for metabolic syndrome could identify people with a greater risk of cardiovascular disease in adulthood, enabling focused therapy. Although abnormalities in risk variables such as hyperglycemia, hypertension, and dyslipidemia must continue to be addressed separately within a given patient, there may be added risk from processes underlying MetS. (e.g., inflammation, oxidative stress, and cellular dysfunction). Yifei Feng et al.[25] investigated the association between the Metabolic Score for Visceral Fat (METS-VF) and the risk of type 2 diabetes mellitus (T2DM) and compared the METS-predictive VF's value for T2DM incidence with other obesity indicators in Chinese adults. Sensitivity and subgroup analyses, respectively, revealed positive relationships. All participants exhibited a significant nonlinear dose-response association between METS-VF and T2DM risk ($^P nonlinearity = 00347$). The METS-VF AUC value for predicting T2DM was the highest among the six indices. The METS-VF may be a reliable and appropriate predictor of T2DM occurrence in Chinese individuals, irrespective of gender, age, or BMI. As the only risk prediction tool evaluated that does not rely on observed biological data, the ROC curve for the FINDRISC score indicates that this could be a useful screening tool in this population. [26,1]

When Hba1c or FPG were added, however, the FINDRISC score beat the metabolic syndrome. In a two-step screening paradigm for diabetes, it may be preferable to utilize the FINDRISC score plus HbA1c (with the official cutoff for diabetes) rather than the metabolic syndrome.[26,2]. While the MetS is a good predictor of incident diabetes, these data imply that in this cohort, a single blood glucose measurement

was more predictive of diabetes than the MetS. [26,3]. Additional potential ways for establishing that the MetS independently predicts diabetes are factor analysis and assessment of statistical interactions. Factor analysis can find clustering of MetS components, but cannot determine if the detected clustering is independently linked with clinical outcomes, and statistical interactions for dichotomous outcomes are functionally limited to two-way interactions. [27]Adolescence MetS and certain MetS component combinations predicted T2DM in early adulthood. Consequently, adolescents, particularly females, with MetS component combinations and a family history of T2DM may be addressed for lifestyle control. [28] Despite the unpredictability of adolescence MetS over 24 years, early to middle adulthood T2DM was predicted by Magnussen et al.[29] the findings are similarly consistent with those of the National Growth and Health Survey, which showed that elevated insulin levels and MetS in childhood independently predicted impaired fasting glucose and T2DM 14 years later. The function of metabolic syndrome in diabetic patients is a topic that, according to many, cannot be neglected. According to Alexander et al[30], metabolic syndrome is an extraordinarily helpful clinical tool for predicting diabetes and CVD, particularly in high-risk individuals with metabolic syndrome that includes IFG. It is essential to exclude diabetes mellitus from metabolic syndrome to maximize the CVD preventive benefit in patients with a history of diabetes mellitus. [31] Aboriginal Canadians had a three- to fivefold greater frequency of diabetes than non-Aboriginal Canadians and metabolic syndrome was related to incident diabetes[32,1]. The lack of the condition at baseline was likely to correctly identify non-diabetic patients. Metabolic syndrome is not a diagnostic tool; nonetheless, the syndrome and its components can be used to convey the elevated risk of diabetes to individuals in rural Aboriginal communities where the

*Eur. Chem. Bull. **2023**,12(Special Issue 1, Part-B), 4782-4792*

4787

oral glucose tolerance test is unavailable. [32,2]. In the natural history of the MetS, dyslipidemia and hypertension appear to be the most important developing components. Additionally, in this chain, the combination of dyslipidemia with obesity or hyperglycemia appears to be the most likely combination that influences the future status of individuals[33].

CLINICAL INTERPRETATION AND MANAGEMENT

The Diabetes Prevention Program randomized trial showed that comprehensive lifestyle modification and metformin medication can lower both the incidence and prevalence of metabolic syndrome at follow-up. [34]Several randomized controlled trials have demonstrated that lifestyle modification can lower metabolic syndrome prevalence.[35,36]. Early diagnosis of individuals at high risk for type 2 diabetes is crucial not only for preventing diabetes, but also for decreasing cardiovascular complications. As previously stated, metabolic syndrome is an ideal indicator of incident diabetes. With the addition of diabetes to the criteria, metabolic syndrome loses its clinical value as a predictor of diabetes development. Therefore, careful consideration should be given to excluding diabetes from the definition, and more attention should be paid to the role of metabolic syndrome as a tool for preventing diabetes. IFG is obviously superior among the five components of metabolic syndrome for its capacity to predict incident diabetes[37,1]; the other components can predict CVD better or similar to IFG[37,2]. Hence, metabolic syndrome and Impaired fasting glucose are complementary, allowing for the prediction of cardiovascular disease and diabetes; the management of these groups requires additional care. As a result, the value of metabolic syndrome in diabetics is much lower than its value in non-diabetic individuals. Some persons with prediabetes have metabolic syndrome, an undeniable macrovascular disease risk factor. Additionally, pre-diabetes develop with age, and aging itself is associated with increased risk. Lifestyle intervention is the first-line treatment for hypertension: weight loss in obese patients, lower intakes of saturated and trans-fatty acids, cholesterol, and sodium, and increased physical activity. The focus must be devoted to lowering insulin resistance. This is best achieved by lifestyle intervention—weight loss and increased physical exercise. Reducing insulin resistance should be a top priority. This is best achieved by lifestyle intervention—weight loss and increased physical exercise [38].

SUMMARY

Metabolic syndrome is a worldwide epidemic and a longtime hazard component The First-degree relative of human beings with an excessive threat of growing diabetes and prediabetes are identifiable primarily based totally on the MetS Z-score. Accordingly, suitable interventions at an in advance level in MetS can be taken into consideration as a powerful approach for stopping the improvement of diabetes and prediabetes in any such excessive-danger population., The incidence of glucose intolerance (PreDM or diabetes) and MetS turned extraordinarily excessive in reputedly healthful humans. Since each PreDM and MetS boom the hazard of diabetes and cardiovascular disease, early detection through a fitness check-up at the ideal time is essential. Moreover, individuals with PreDM and MetS validated capabilities suggestive of insulin resistance phenotypes. Future research inspecting the improvement and prevention of diabetes in those specific clusters is needed. The American Diabetic Association reintroduced pre-diabetes in 2005 to include IGT and IFG but not other diabetes risk factors. As a linear measure, MetS severity predicts T2DM and prediabetes. Metformin and comprehensive lifestyle modification reduced metabolic

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4788

syndrome incidence and prevalence at follow-up in the Diabetes Prevention Program randomised trial. Early type 2 diabetes diagnosis prevents cardiovascular disease. These data suggest a potential clinical use for monitoring MetS severity over time and provide evidence that MetS severity is a marker of disease risk. As a drawn-out indicator of T2DM and CVD, the seriousness of MetS showed steady free relationships and Adolescences MetS and a few mixes of MetS parts anticipated early adulthood T2DM. This backs up the clinical use of MetS severity as a way to predict future disease risk.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist and no conflict of interests in publishing this paper.

REFERENCES

1. Tangjittipokin W, Srisawat L, Teerawattanapong N, Narkdontri T, Homsanit M, Plengvidhya N. Prevalence and Characteristics of Prediabetes and Metabolic Syndrome in Seemingly Healthy Persons at a Health Check-Up Clinic. Journal of Multidisciplinary Healthcare. 2022 Jan 1:1585-94.

2. Regufe VM, Pinto CM, Perez PM. Metabolic syndrome in type 2 diabetic patients: A review of current evidence. Porto biomedical journal. 2020 Nov;5(6).

3. John A. Morrison, PhD,Lisa Aronson Friedman, ScM, Ping Wang, PhD, Charles J. Glueck, MD Metabolic Syndrome in Childhood Predicts Adult Metabolic Syndrome and Type 2 Diabetes Mellitus 25 to 30 Years Later.2007 November VOLUME 152, ISSUE 2, P201-206 DOI:https://doi.org/10.1016/j.jpeds.2007.09.010

4. Alberti KG. Screening and diagnosis of prediabetes: where are we headed?. Diabetes, Obesity and Metabolism. 2007 Sep;9:12-6.

5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2010 Jan 1;33(Supplement_1):S62-9.

6. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2005 Sep 1;28(9):2289-304.

7. Palaniappan L, Carnethon MR, Wang Y, Hanley AJ, Fortmann SP, Haffner SM, Wagenknecht L. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. Diabetes care. 2004 Mar 1;27(3):788-93.

8. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes care. 2008 Sep 1;31(9):1898-904.

9. Nishimura R, Nakagami T, Tominaga M, Yoshiike N, Tajima N. Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan. Diabetes research and clinical practice. 2007 Oct 1;78(1):77-84.

10. Saklayen MG. The global epidemic of the metabolic syndrome. Current hypertension reports. 2018 Feb;20(2):1-8.

11. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clinics in dermatology. 2018 Jan 1;36(1):14-20.

12. Meamar R, Amini M, Aminorroaya A, Nasri M, Abyar M, Feizi A. Severity of the metabolic syndrome as a predictor of prediabetes and type 2 diabetes in first degree relatives of type 2 diabetic patients: A 15-year prospective cohort

Eur. Chem. Bull. 2023,12(Special Issue 1, Part-B), 4782-4792

4789

study. World Journal of Diabetes. 2020 May 5;11(5):202.

13. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR, Kronmal R, Liu K, Saad M. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. JACC: Cardiovascular Imaging. 2012 Apr;5(4):358-66.

14. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. Diabetologia. 2015 Dec;58:2745-52.

15. Lee AM, Fermin CR, Filipp SL, Gurka MJ, DeBoer MD. Examining trends in prediabetes and its relationship with the metabolic syndrome in US adolescents, 1999–2014. Acta diabetologica. 2017 Apr;54:373-81.

16. DeBoer MD, Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Pearson TA. Independent associations between metabolic syndrome severity and future coronary heart disease by sex and race. Journal of the American College of Cardiology. 2017 Mar 7;69(9):1204-5.

17. Gurka MJ, Ice CL, Sun SS, DeBoer MD. A confirmatory factor analysis of the metabolic syndrome in adolescents: an examination of sex and racial/ethnic differences. Cardiovascular Diabetology. 2012 Dec;11:1-0.

18. Gurka MJ, Lilly CL, Oliver MN, DeBoer MD. An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. Metabolism. 2014 Feb 1;63(2):218-25.

19. Siewert S, Filipuzzi S, Codazzi L, Gonzalez I, Ojeda MS. Impact of metabolic syndrome risk factors in

first-degree relatives of type 2 diabetic patients. The review of diabetic studies: RDS. 2007;4(3):177.

20. Mirbolouk M, Derakhshan A, Charkhchi P, Guity K, Azizi F, Hadaegh F. Incidence and predictors of early adulthood pre-diabetes/type 2 diabetes, among Iranian adolescents: The Tehran lipid and glucose study. Pediatric Diabetes. 2016 Dec;17(8):608-16.

21. Tangjittipokin W, Srisawat L, Teerawattanapong N, Narkdontri T, Homsanit M, Plengvidhya N. Prevalence and Characteristics of Prediabetes and Metabolic Syndrome in Seemingly Healthy Persons at a Health Check-Up Clinic. Journal of Multidisciplinary Healthcare. 2022 Jan 1:1585-94.

22. Ghachem A, Brochu M, Dionne IJ. Differential clusters of modifiable risk factors for impaired fasting glucose versus impaired glucose tolerance in adults 50 years of age and older. Therapeutic Advances in Chronic Disease. 2019 Jun;10:2040622319854239.

23. Wang R, Zhang P, Li Z, Lv X, Cai H, Gao C, Song Y, Yu Y, Li B, Cui Y. The prevalence of pre-diabetes and diabetes and their associated factors in Northeast China: a cross-sectional study. Scientific reports. 2019 Feb 21;9(1):2513.

24. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. The Journal of pediatrics. 2008 Feb 1;152(2):201-6.

25. HUANG TT, MORRISON JA, ARONSON FRIEDMAN L, WANG P, GLUECK CJ. Metabolic Syndrome in Childhood Predicts Adult Metabolic Syndrome and Type 2 Diabetes Mellitus 25 to 30 Years Later.

Eur. Chem. Bull. **2023**,*12(Special Issue 1, Part-B), 4782-4792*

4790

Commentary. The Journal of pediatrics. 2008;152(2).

26. Feng Y, Yang X, Li Y, Wu Y, Han M, Qie R, Huang S, Wu X, Zhang Y, Zhang J, Hu H. Metabolic Score for Visceral Fat: a novel predictor for the risk of type 2 diabetes mellitus. British Journal of Nutrition. 2022 Sep;128(6):1029-36.

27. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. American journal of epidemiology. 2002 Dec 1;156(11):1070-7.

28. Stephen C, Michael W, Peggy A, Michael N, William HD. Prevalence of a Metabolic Syndrome Phenotype in Adolescents. Archives of Pediatrics & Adolescent Medicine. 2003 Aug 1;157(8):821.

29. Asghari G, Hasheminia M, Heidari A, Mirmiran P, Guity K, Shahrzad MK, Azizi F, Hadaegh F. Adolescent metabolic syndrome and its components associations with incidence of type 2 diabetes in early adulthood: Tehran lipid and glucose study. Diabetology & Metabolic Syndrome. 2021 Dec;13(1):1-9.

30 Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, Kivimäki M, Mattsson N, Kähönen M, Laitinen T, Taittonen L. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. Circulation. 2010 Oct 19;122(16):1604-11.

31. Alexander CM, Landsman PB, Grundy SM. Metabolic syndrome and hyperglycemia: congruence and divergence. American Journal of Cardiology. 2006 Oct 1;98(7):982-5.

32. Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, Lee WC, Kang MI, Yim HW, Yoon KH, Son HY. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. Journal of diabetes investigation. 2013 Jul;4(4):334-43.

33. Ley SH, Harris SB, Mamakeesick M, Noon T, Fiddler E, Gittelsohn J, Wolever TM, Connelly PW, Hegele RA, Zinman B, Hanley AJ. Metabolic syndrome and its components as predictors of incident type 2 diabetes mellitus in an Aboriginal community. Cmaj. 2009 Mar 17;180(6):617-24.

34. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S, Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Annals of internal medicine. 2005 Apr 19;142(8):611-9.

35. Bo S, Ciccone G, Baldi C, Benini L, Dusio F, Forastiere G, Lucia C, Nuti C, Durazzo M, Cassader M, Gentile L. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. Journal of general internal medicine. 2007 Dec;22:1695-703.

36. Ilanne-Parikka P, Eriksson JG, Lindstrom J, Peltonen M, Aunola S, Hamalainen HE, Keinanen-Kiukaanniemi S, Laakso M, Valle TT, Lahtela J, Uusitupa M. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes

*Eur. Chem. Bull. **2023**,12(Special Issue 1, Part-B), 4782-4792*

4791

Prevention Study. Diabetes care. 2008 Apr 1;31(4):805-7.

37. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005 Nov 15;112(20):3066-72.

38. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes care. 2007 Mar 1;30(3):753-9

*Eur. Chem. Bull. **2023**,12(Special Issue 1, Part-B), 4782-4792*

4792