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Editorial

Useful Biomarkers of Metabolic Syndrome

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1. Introduction

The Special Issue call for papers on "Metabolic syndrome and its association with biomarkers" was proposed to present research on various markers for pathophysiology and the early detection of metabolic syndrome (MetS).

MetS is a cluster of risk factors for developing heart disease, stroke, and type 2 diabetes [1]. Visceral adiposity and insulin resistance are crucial mechanisms of MetS [2,3].

After the WHO group defined MetS in 1998 [4], efforts to unify the definition of MetS have been continued in accredited organizations. However, various diagnostic criteria are still being used in research [5–7]. MetS is usually diagnosed when three or more risk factors are present among abdominal obesity, high blood pressure, hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein cholesterol levels [7].

Numerous biomarkers have been discovered to better understand the pathophysiology and detect MetS early, including adipokines and inflammatory markers. We would like to present clinically useful Mets biomarkers with sufficient evidence.

2. Useful Biomarkers of Metabolic Syndrome

2.1. Adipokines

Leptin is a hormone that regulates energy metabolism by suppressing food intake and increasing energy expenditure, and is known to be related to abdominal obesity and insulin resistance, which are essential factors for MetS [8]. In large-scale cross-sectional studies, leptin levels were significantly positively associated with MetS [9–11]. The significant association between leptin and MetS presented after adjusting covariates, including age, insulin resistance marker, and body mass index (BMI) [9]. In addition, high leptin levels have been suggested as a predictive marker of developing MetS in prospective studies [12–14].

Adiponectin improves glucose metabolism and regulates dietary intake and energy expenditure [15]. Low serum adiponectin levels were associated with MetS in many cross-sectional studies [16,17]. In a study including Japanese adults, an adiponectin cutoff value of 4 μg/mL identified most subjects with MetS [17]. Prospective studies suggest the usefulness of adiponectin in predicting Met [18,19]. After a median follow-up of 9.4 years, 1134 healthy participants with low levels of adiponectin (quartile 1) at baseline had an approximately three-fold increased risk of developing MetS compared to those with high levels (quartile 4). Participants who decreased adiponectin levels during follow-up had more than a four-fold increased risk of MetS after multivariate adjustment [19].

High-molecular-weight (HMW) adiponectin, the active form of adiponectin, is a more useful marker than total adiponectin for predicting developing MetS [20]. Low HMW adiponectin levels ($\leq$2.65 μg/mL) were associated with progression to MetS.

Since leptin and adiponectin are independent factors of MetS and have opposing functions in fat metabolism, the leptin to adiponectin (LA) ratio is suggested as a better marker

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for MetS than adiponectin or leptin alone [21]. A recent prospective study evaluating the association of leptin, adiponectin, and LA rates with future risk of MetS in middle-aged and elderly Koreans showed that leptin, adiponectin levels, and LA rates could be helpful to biomarkers for predicting future MetS incidence [14].

2.2. Inflammatory and Oxidative Stress Biomarkers

C-reactive protein (CRP) is a non-specific biomarker commonly used in the evaluation of disease activity, diagnosis, and management of infection, as well as in the differential diagnosis or classification of inflammatory diseases in inflammatory diseases such as rheumatic diseases [22]. Elevated CRP is associated with metabolic disease, including dyslipidemia, diabetes, and metabolic syndrome [23]. In a cross-sectional study in Germany, the age-adjusted geometric means of CRP concentrations in subjects grouped according to the presence of 0–1, 2–3, and 4–5 features of MetS were 1.11, 1.27, and 2.16 mg/L, respectively, with a statistically significant trend [24]. A prospective study evaluating interrelationships between CRP, MetS, and incident cardiovascular events among 14,719 healthy women who were followed up over 8-year follow-up showed CRP works as a prognostic factor on subsequent risk at all severity levels of MetS [25]. In this study, the cutoff point for CRP to differentiate between high-risk and low-risk groups was 3 mg/L. Many studies demonstrate that CRP can be used as a helpful biomarker in MetS.

Ferritin is a vital iron storage protein that regulates iron homeostasis and can reflect the degree of acute and chronic inflammation [26]. A cross-sectional study including 18,581 men showed that the risk of MetS increased about two times in the highest ferritin quartile ($\geq$212.8 ng/mL) compared to the lowest ferritin quartile (<107.3 ng/mL) [27]. Another study of postmenopausal women showed that the OR of the highest ferritin quartile ($\geq$86.0 ng/mL) for MetS was about two times, compared to the lowest quartile ($\leq$36.3 ng/mL), after adjustment for age, smoking, alcohol intake, and regular exercise [28]. The usefulness of ferritin as a biomarker of MetS also showed consistent results in prospective studies [29]. A meta-analysis of 15 observational studies concluded that increased ferritin levels are independently and positively associated with the presence of MetS [30].

Gamma-glutamyltransferase (GGT) is a ubiquitous enzyme in human tissues, including the kidney, pancreas, liver, spleen, heart, and brain, that recycles precursors to the antioxidant and metabolic substrate glutathione (GSH). GGT has been studied as a predictor of MetS, diabetes, hypertension, and stroke risk, and used as a biomarker to evaluate alcohol consumption and hepatobiliary disease [31,32]. A cross-sectional analysis suggested the cutoff value of GGT for MetS was 27 IU/L for men and 17 IU/L for women [33]. Increased serum GGT could predict the onset of metabolic syndrome and the occurrence of CVD and death above and beyond traditional cardiac risk factors, including CRP. The highest GGT quartile experienced a 67% increase in CVD incidence [33].

Uric acid is the end metabolite produced by the breakdown of purines, which are chemicals that enter the bloodstream during the digestion of foods or from the normal breakdown of some of the body's cells. High uric acid is positively associated with obesity, MetS, type 2 diabetes, and CVDs [34]. In a cross-sectional study using a nationally representative sample of US adults, the prevalence of MetS was 18.9% for uric acid levels less than 6 mg/dL, 59.7% for uric acid levels from 8–8.9 mg/dL, and 70.7% for uric acid levels of 10 mg/dL or greater, and the increasing trends persisted in subgroups adjusted by sex, age group, alcohol intake, body mass index, hypertension, and diabetes [35]. A prospective cohort study including the Korean adult population showed that a high uric acid level could be a positive predictor for MetS for a 2.6-year follow-up period [36]. A dose–response meta-analysis of a prospective study suggested that each 1 mg/dL increase in serum uric acid was linearly associated with MetS risk (RR, 1.30; 95% CI, 1.22–1.38), suggesting that uric acid has proven to be a useful biomarker [37].

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References

1. Saklayen, M.G. The global epidemic of the metabolic syndrome. *Curr. Hypertens. Rep.* **2018**, *20*, 1–8.
2. Zafar, U.; Khaliq, S.; Ahmad, H.U.; Manzoor, S.; Lone, K.P. Metabolic syndrome: An update on diagnostic criteria, pathogenesis, and genetic links. *Hormones* **2018**, *17*, 299–313. [CrossRef] [PubMed]
3. Oda, E. Historical perspectives of the metabolic syndrome. *Clin. Dermatol.* **2018**, *36*, 3–8. [CrossRef]
4. Alberti, K.G.M.M.; Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet. Med.* **1998**, *15*, 539–553. [CrossRef]
5. Zimmet, P.; Alberti, K.; Shaw, J. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome. *Diabetes Voice* **2005**, *50*, 31–33.
6. Grundy, S.M.; Cleeman, J.I.; Daniels, S.R.; Donato, K.A.; Eckel, R.H.; Franklin, B.A.; Gordon, D.J.; Krauss, R.M.; Savage, P.J.; Smith, S.C., Jr.; 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. [CrossRef] [PubMed]
7. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.C.; James, W.P.; Loria, C.M.; Smith, S.C., Jr. Harmonizing the metabolic syndrome: A joint interim statement of the international 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.
8. Friedman, J. Leptin at 20: An overview. *J. Endocrinol.* **2014**, *223*, T1–T8. [CrossRef]
9. Esteghamati, A.; Noshad, S.; Khalilzadeh, O.; Morteza, A.; Nazeri, A.; Meysamie, A.; Nakhjavani, M. Contribution of serum leptin to metabolic syndrome in obese and nonobese subjects. *Arch. Med. Res.* **2011**, *42*, 244–251.
10. Yun, J.E.; Kimm, H.; Jo, J.; Jee, S.H. Serum leptin is associated with metabolic syndrome in obese and nonobese Korean populations. *Metabolism* **2010**, *59*, 424–429. [CrossRef]
11. Madeira, I.; Bordallo, M.A.; Rodrigues, N.C.; Carvalho, C.; Gazolla, F.; Collett-Solberg, P.; Medeiros, C.; Bordallo, A.P.; Borges, M.; Monteiro, C.; et al. Leptin as a predictor of metabolic syndrome in prepubertal children. *Arch. Endocrinol. Metab.* **2017**, *61*, 7–13. [CrossRef] [PubMed]
12. Franks, P.W.; Brage, S.; Luan, J.; Ekelund, U.; Rahman, M.; Farooqi, S.; Halsall, I.; O'Rahilly, S.; Wareham, N.J. Leptin predicts a worsening of the features of the metabolic syndrome independently of obesity. *Obes. Res.* **2005**, *13*, 1476–1484. [CrossRef] [PubMed]
13. Ukkola, O.; Kesäniemi, Y.A. Leptin and high-sensitivity C-reactive protein and their interaction in the metabolic syndrome in middle-aged subjects. *Metabolism* **2007**, *56*, 1221–1227. [CrossRef]
14. Lee, K.W.; Shin, D. Prospective associations of serum adiponectin, leptin, and leptin-adiponectin ratio with incidence of metabolic syndrome: The korean genome and epidemiology study. *Int. J. Environ. Res. Public Health* **2020**, *17*, 3287. [CrossRef] [PubMed]
15. Stofkova, A. Leptin and adiponectin: From energy and metabolic dysbalance to inflammation and autoimmunity. *Endocr. Regul.* **2009**, *43*, 157–168. [PubMed]
16. Saely, C.H.; Risch, L.; Hoefle, G.; Rein, P.; Muendlein, A.; Marte, T.; Aczel, S.; Langer, P.; Drexel, H. Low serum adiponectin is independently associated with both the metabolic syndrome and angiographically determined coronary atherosclerosis. *Clin. Chim. Acta* **2007**, *383*, 97–102. [CrossRef] [PubMed]
17. Ryo, M.; Nakamura, T.; Kihara, S.; Kumada, M.; Shibazaki, S.; Takahashi, M.; Nagai, M.; Matsuzawa, Y.; Funahashi, T. Adiponectin as a biomarker of the metabolic syndrome. *Circ. J.* **2004**, *68*, 975–981. [CrossRef]
18. Ahonen, T.; Saltevo, J.; Kautiainen, H.; Kumpusalo, E.; Vanhala, M. The association of adiponectin and low-grade inflammation with the course of metabolic syndrome, Nutrition. *Metab. Cardiovasc. Dis.* **2012**, *22*, 285–291. [CrossRef]
19. Lindberg, S.; Jensen, J.; Bjerre, M.; Frystyk, J.; Flyvbjerg, A.; Jeppesen, J.; Mogelvang, R. Low adiponectin levels at baseline and decreasing adiponectin levels over 10 years of follow-up predict risk of the metabolic syndrome. *Diabetes Metab.* **2017**, *43*, 134–139. [CrossRef]
20. Seino, Y.; Hirose, H.; Saito, I.; Itoh, H. High-molecular-weight adiponectin is a predictor of progression to metabolic syndrome: A population-based 6-year follow-up study in Japanese men. *Metabolism* **2009**, *58*, 355–360. [CrossRef]
21. Falahi, E.; Rad, A.H.K.; Roosta, S. What is the best biomarker for metabolic syndrome diagnosis? *Diabetes Metab. Syndr. Clin. Res. Rev.* **2015**, *9*, 366–372. [CrossRef] [PubMed]
22. Pepys, M.B.; Hirschfield, G.M. C-reactive protein: A critical update. *J. Clin. Investig.* **2003**, *111*, 1805–1812. [CrossRef] [PubMed]
23. Jeong, H.; Baek, S.-Y.; Kim, S.W.; Park, E.-J.; Lee, J.; Kim, H.; Jeon, C.H. C reactive protein level as a marker for dyslipidaemia, diabetes and metabolic syndrome: Results from the Korea National Health and Nutrition Examination Survey. *BMJ Open* **2019**, *9*, e029861. [CrossRef] [PubMed]

24. Fröhlich, M.; Imhof, A.; Berg, G.; Hutchinson, W.L.; Pepys, M.B.; Boeing, H.; Muche, R.; Brenner, H.; Koenig, W. Association between C-reactive protein and features of the metabolic syndrome: A population-based study. *Diabetes Care* **2000**, *23*, 1835–1839. [CrossRef] [PubMed]
25. Ridker, P.M.; Buring, J.E.; Cook, N.R.; Rifai, N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow-up of 14 719 initially healthy American women. *Circulation* **2003**, *107*, 391–397. [CrossRef]
26. Kernan, K.F.; Carcillo, J.A. Hyperferritinemia and inflammation. *Int. Immunol.* **2017**, *29*, 401–409. [CrossRef]
27. Ryoo, J.H.; Kim, M.G.; Lee, D.W.; Shin, J.Y. The relationship between serum ferritin and metabolic syndrome in healthy Korean men. *Diabetes Metab. Res. Rev.* **2011**, *27*, 597–603. [CrossRef]
28. Cho, M.R.; Park, J.K.; Choi, W.J.; Cho, A.R.; Lee, Y.J. Serum ferritin level is positively associated with insulin resistance and metabolic syndrome in postmenopausal women: A nationwide population-based study. *Maturitas* **2017**, *103*, 3–7. [CrossRef]
29. Vari, I.S.; Balkau, B.; Kettaneh, A.; André, P.; Tichet, J.; Fumeron, F.; Caces, E.; Marre, M.; Grandchamp, B.; Ducimetière, P.; et al. Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in a general population: Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). *Diabetes Care* **2007**, *30*, 1795–1801. [CrossRef]
30. Abril-Ulloa, V.; Flores-Mateo, G.; Solà-Alberich, R.; Manuel-y-Keenoy, B.; Arija, V. Ferritin levels and risk of metabolic syndrome: Meta-analysis of observational studies. *BMC Public Health* **2014**, *14*, 483. [CrossRef]
31. Onat, A.; Can, G.; Örnek, E.; Çiçek, G.; Ayhan, E.; Doğan, Y. Serum γ-glutamyltransferase: Independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. *Obesity* **2012**, *20*, 842–848. [CrossRef] [PubMed]
32. Yang, W.; Kim, C.K.; Kim, D.Y.; Jeong, H.G.; Lee, S.H. Gamma-glutamyl transferase predicts future stroke: A Korean nationwide study. *Ann. Neurol.* **2018**, *83*, 375–386. [CrossRef] [PubMed]
33. Lee, D.S.; Evans, J.C.; Robins, S.J.; Wilson, P.W.; Albano, I.; Fox, C.S.; Wang, T.J.; Benjamin, E.J.; D'Agostino, R.B.; Vasan, R.S. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: The Framingham Heart Study. *Arter. Thromb. Vasc. Biol.* **2007**, *27*, 127–133. [CrossRef] [PubMed]
34. Jeong, J.; Suh, Y.J. Association between Serum Uric Acid and Metabolic Syndrome in Koreans. *J. Korean Med. Sci.* **2019**, *34*, e307. [CrossRef] [PubMed]
35. Choi, H.K.; Ford, E.S. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am. J. Med.* **2007**, *120*, 442–447. [CrossRef]
36. Yadav, D.; Lee, E.S.; Kim, H.M.; Choi, E.; Lim, J.S.; Ahn, S.V.; Koh, S.B.; Chung, C.H. Prospective study of serum uric acid levels and incident metabolic syndrome in a Korean rural cohort. *Atherosclerosis* **2015**, *241*, 271–277. [CrossRef]
37. Yuan, H.; Yu, C.; Li, X.; Sun, L.; Zhu, X.; Zhao, C.; Zhang, Z.; Yang, Z. Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-Analysis of Prospective Studies. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 4198–4207. [CrossRef]