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Contents

Monthly Volume 11 Number 2 February 15, 2020

EDITORIAL

ORIGINAL ARTICLE

Case Control Study

Contents

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Volume 11 Number 2 February 15, 2020

ABOUT COVER

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EDITORIAL

Weight loss induced by whole grain-rich diet is through a gut microbiota-independent mechanism

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Abstract

The prevalence of overweight and obesity has increased worldwide. Obesity is a well-known risk factor of type 2 diabetes mellitus and cardiovascular disease and raises public health concerns. Many dietary guidelines encourage the replacement of refined grains with whole grains (WGs) to enhance body weight management. Current evidence regarding interrelationships among WGs, body weight, and gut microbiota is limited and inconclusive. In this editorial, we comment on the article by Roager *et al* published in the recent issue of the *Gut* 2019; 68(1): 83-93. In the study, obese patients (25 < body mass index < 35 kg/m^2) were randomly assigned to receive two 8-wk dietary controlling periods with WGs and refined grain-rich diet. The results showed significantly decreased body weight in the WG group. Either the composition of gut microbiota or short-chain fatty acids, the leading end product of fermentation of non-digestible carbohydrate by gut microbiota, did not differ between the two groups. The study highly indicated that a WG-rich diet reduced body weight independent of gut microbiota. We then raised some plausible mechanisms of how WGs might influence body weight and demonstrated more literature in line with WGs enhance body weight control through a microbiota-independent pathway. Possible mechanisms include: (1) The abundant dietary fiber contents of WGs increase satiety, satiation, energy excretion from stool, and energy expenditure

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simultaneously decreasing energy absorption and fat storage; (2) The plentiful amount of polyphenols of WGs improve energy expenditure by hampering adipocyte maturation and function; (3) The sufficient magnesium and zinc of WGs guarantee lean body mass growth and decrease fat mass; (4) The effect of WGs on brown adipose tissue is a key component of non-shivering thermogenesis; and (5) The increase of adiponectin by WGs enhances glucose utilization, lipid oxidation, and energy expenditure.

Key words: Whole grain; Obesity; Microbiota; Short-chain fatty acids; Brown adipose tissue; Adiponectin

Core tip: Obesity and its co-morbidity have caused worldwide public health concerns. Many countries recommend substituting whole grain (WG) for refined grain. Roager *et al* concluded that WGs reduce body weight through a microbiota-independent pathway. We suggest that the abundant dietary fibers, the plentiful amount of minerals and polyphenols of WGs, and possible effects on brown adipose tissue and adiponectin might take part in the weight loss caused by WG diet consumption.

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INTRODUCTION

A grain has three key components – the endosperm, germ, and bran. A whole grain (WG) contains these three parts in natural proportion, while a refined grain misses at least one part[1]. The 2015 Dietary Guideline Advisory Committee viewed higher WG consumption as a healthy diet pattern and even recommended that the United States population substitute WGs for most refined grains[2]. It is widely accepted that WGs improve health outcomes such as all-cause mortality and reduce risks of life-style related diseases, including type 2 diabetes mellitus, cardiovascular disease, coronary heart diseases, and stroke[3-5]. Gut microbiota is a recently rising star candidate, as it is considered to play an essential role in the abovementioned effects[6]. Gut microbiota has also been shown to be a novel treatment target and moderator of obesity[7,8]. Some reports have suggested that increased WG consumption alters the diversity, number, or proportion of gut microbiome, further benefiting health outcomes[9-12]. However, other studies have concluded that the WG diet does not affect gut microbiota at all[13-16]. To date, evidence regarding the association among WG consumption, body weight change, and gut microbiome is not only limited but also inconclusive[17-19]. Thus we read with great interest the article by Roager *et al*[20] entitled "Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomized cross-over trial" published in the *Gut* 2019, to determine whether enriched WG consumption alters body weight, and if so, if it is via the gut-microbiome-pathway.

ABOUT THE SELECTED ARTICLE

Roager *et al*[20] aimed to determine if the WG-rich diet influences the gut microbiome or body weight. They enrolled 50 non-morbidly obese patients [body mass index (BMI) between 25 and 35 kg/m^2] who received two 8-wk dietary controlling periods with a WG and refined grain-rich diet. The intake of WG was 179 ± 50 g/d and 13 ± 10 g/d during the WG and refined grain diet periods, respectively. The washout period was 6 wk between the two periods. Anthropometry, blood pressure, metabolic markers, gut permeability assessment, intestinal transit time, and urinary metabolic profiles were documented. Fecal shotgun sequencing-based metagenomics, as well as 16S rRNA amplification, were used to examine the gut microbiome. The results clearly showed a significantly decreased body weight (P < 0.001) corresponding to

enriched WG consumption. On the other hand, the composition of gut microbiome did not differ between the two groups.

Short-chain fatty acids (SCFAs) are the main end products of gut microbiota fermentation of non-digestive carbohydrates of WGs, which escape digestion and absorption in the intestines[7,21,22]. In the study, the effects of WG and refined-grain-rich diets on plasma SCFAs levels were minimal, which again support the assumption that the gut microbiota does not change much after WG diet intake, thereby indicating that weight loss induced by a WG-rich diet is through a gut microbiome-independent mechanism.

However, the authors did not directly compare the relationship between the plasma concentration of SCFAs and body weight change or inflammation markers. A weak connection between SFCAs and body weight would provide evidence that WG intake reduces body weight via a microbiome-independent pathway.

POSSIBLE MECHANISMS OF BODY WEIGHT LOSS CAUSED BY A WG DIET

If not through the microbiota, what could be the possible mechanisms of body weight loss caused by a WG-rich diet? WGs contain more dietary fibers than refined grains. Dietary fibers are classified as insoluble fibers and soluble (viscous) fibers. First, the lower digestible energy per unit mass of WGs results in lower energy intake[23]. Second, the greater size of starch particles of WGs takes more chewing effort and time, which lead to more oro-sensory stimulation and satiation[24]. Third, the large volume of fibers increases gastric distention and mechanoreceptor-mediated signals of satiation and satiety[24,25]. Fourth, soluble fibers, mostly derived from WGs, rather than from fruits or vegetables, physiologically induce the release of gut hormones secreted by enteroendocrine cells, such as peptide YY, cholecystokinin, and glucagon-like peptide-1, which are involved in glucose homeostasis and energy balance[26-29,31]. Not only the viscous fiber itself, but also the gut hormones mentioned above prolong gastrointestinal transit time and delay gastric emptying, consequently increasing satiety and inducing body weight loss[22,24,30,31]. Furthermore, fibers from WGs build up intestinal physical barriers, thus delaying absorption of glucose and fatty acid in the intestine and decreasing fat storage[22,24,25,29].

In the study by Roager *et al*[20], energy consumption in the WG group was significantly lower than that in the refined grain group. Suhr *et al*[32]. conducted a 6-wk, randomized-controlled, parallel-arm trial involving 70 non-morbidly obese patients who received a refined grain-, WG wheat-, and WG rye-based diet. Body weight decreased more in the WG rye group than in the refined grain group (-1.06 ± 1.60 and +0.15 ± 1.28 kg, respectively; $P < 0.01$). Energy consumption of the WG rye group was about 200 kcal lower than that of the refined grain group ($P < 0.05$). These results added to the evidence that the abundant dietary fibers in WGs help body weight management due to increase satiation and satiety.

Except via gut hormones, WGs might influence energy metabolism by maintenance of stool passage and increasing formation of bulkier stool[30], which lead to higher energy loss from defecation. WGs are an essential source of dietary magnesium, which helps the human body avoid constipation. In a randomized controlled study[33] including 81 healthy men and postmenopausal women divided into the WG group and refined grain group, stool characteristics including stool weight and energy, resting metabolic rate (RMR), and gut microbiota composition were examined. The diversity of microbiota did not differ between the two groups. The subjects in the WG group had significantly increased stool energy content ($P < 0.0001$) and stool weight ($P = 0.0001$). There was also a strong relationship between RMR and fiber-adjusted stool energy content. The results suggest that WGs might enhance energy expenditure by increasing stool energy excretion without altering the gut microbiome.

Very recently, Allegretti *et al*[34] performed a double-blind, randomized-controlled pilot study in 22 otherwise healthy obese patients (BMI > 35 kg/m^2), who received either capsules containing gut microbes from a lean donor or placebo. The treatment pills were found safe and able to alter the gut microbiota of the recipients. However, early results failed to show a statically significant difference in BMI and gut hormones between intervention and control groups. The above result further supports our hypothesis that the decrease of body weight and the change of gut hormones involved in appetite regulation might be independent of gut microbiota.

WGs contain more polyphenols and minerals such as iron, zinc, magnesium (Mg), selenium in comparison with refined grains[6,35]. Polyphenols interfere with the signaling pathways of adipocyte oxidation, differentiation, and proliferation, further attenuate lipogenesis, enhance lipolysis and energy expenditure[36,37]. Mg acts as a co-

factor of many metabolic reactions and a component of variable enzymes. Some rodent studies revealed that Mg deficiency reduced lean body mass and increased body fat composition[38]. The lower lean body mass caused RMR to decrease. A double-blind, randomized-controlled trial including overweight (BMI 25-30 kg/m^2) women who had taken 250 mg magnesium daily for 8 weeks demonstrated statistically significant reduction of fat mass (P = 0.02) and increase of mean lean body mass (P = 0.05) compared to the baseline measurement data[39]. Zinc depletion was shown to be related to obesity and the decline of circulation leptin levels[40,41]. Both lack of magnesium and zinc could impair the production of insulin-like growth factor-1 and growth hormone[42], therefore decrease lean body mass growth. Although human studies are scarce, it does not exclude the possibility that polyphenols and trace minerals in WGs improve body weight management.

Brown adipose tissue (BAT) is crucial in non-shivering thermogenesis, which includes both cold-induced and diet-induced thermogenesis of human energy expenditure, whereas white adipose tissue (WAT), by contrast, stores excess energy as triglycerides[43]. The stimulation of BAT is now a hot target for obesity. Xiao *et al*[44]. documented that fermented barley promoted WAT beiging and BAT activation, therefore caused body weight loss in rats. Evidence regarding the relationship between BAT and WGs in humans is still limited; more investigations are needed.

Published research suggests that WGs increase adiponectin, which is secreted by adipose tissues, and play essential roles in energy balance, fat metabolism, and glucose homeostasis[45]. It is believed that adiponectin promotes glucose utilization in skeletal muscle, suppresses glucose secretion from liver, and enhances fatty acids oxidation[46]. Additionally, adiponectin acts in hypothalamus and increases corticotrophin-releasing hormone, and further affects thermogenesis and increases energy expenditure[47]. Emerging roles of hepatokines, such as bile acids, fibroblast growth factor-19 and hepassocin, may deserve further investigation[48].

In short, how a WG diet affects body weight regulation is possible as, but not limited to, the following: (1) The abundant dietary fibers of WGs decrease energy intake due to the lower energy density compared with refined grain diet, attenuate bowel fat and glucose absorption, provoke satiation through stimulation of oro-sensory and gastric mechanoreceptors, enhance satiety by causing delay of gastric emptying and elongation of gastrointestinal transit time. (2) The rich content of polyphenols of WGs interfere with adipocyte signaling pathways and increase energy expenditures. (3) WGs are a good source of minerals that are key co-factors in many metabolic reactions. Sufficient Mg and zinc guarantee lean body mass growth and body fat mass decrease. (4) WGs interact with BAT, which is essential in non-shivering thermogenesis. And (5) The effect of WGs on adiponectin promotes glucose utilization, lipid oxidation, and energy expenditure.

CONCLUSION

The mechanism of how the WG-rich diet influences body weight is still ambiguous. Here we suggest that the ability of WGs to decrease body weight is, at least in part, related to multiple microbiota-independent pathways. We summarized the hypothetic pathways in Table 1. Further studies should thoroughly examine if different types of WGs, such as wheat, brown rice, millet, maize, barley, rye, oats, triticale, various population subgroups, the different amount of WG consumption, and different duration of intervention act on the relationship among WG diet, body weight, and gut microbiota. Standardized protocols and new biomarkers regarding changes in the species, diversity, and function of fecal microbiota are in need. Furthermore, more investigations should aim at whether the WG diet improves body weight regulation through the alternation of RMR, gut hormones associated with satiety, BAT, and adiponectin in the future.

Table 1 Possible mechanisms of whole grain diet affect body weight regulation

Mediator	Mechanism
Dietary fibers in WGs	Lower energy density results in less energy intake
	Attenuation of intestinal nutrition absorption
	Stimulation of oro-sensory and gastric mechanoreceptors result in increased satiation
	Delay of gastric emptying and gastrointestinal transition result in increased satiety
Polyphenols in WGs	Interferes with adipocyte signaling pathways results in more energy expenditures
Minerals in WGs	Magnesium and zinc are co-factors in lean body mass growth and body fat mass decrease
Brown adipose tissue	Non-shivering thermogenesis
Adiponectin	Promotes glucose utilization, lipid oxidation, and energy expenditure

WGs: Whole grains.

REFERENCES

1 **de Munter JS**, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Med* 2007; **4**: e261 [PMID: 17760498 DOI: 10.1371/journal.pmed.0040261]

2 **Office of Disease Prevention and Health Promotion**. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Available from: https://health.gov/dietaryguidelines/2015-scientific-report/

3 **Barrett EM**, Batterham MJ, Ray S, Beck EJ. Whole grain, bran and cereal fibre consumption and CVD: a systematic review. *Br J Nutr* 2019; **121**: 914-937 [PMID: 30761962 DOI: 10.1017/S000711451900031X]

4 **Ye EQ**, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr* 2012; **142**: 1304-1313 [PMID: 22649266 DOI: 10.3945/jn.111.155325]

5 **Aune D**, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016; **353**: i2716 [PMID: 27301975 DOI: 10.1136/bmj.i2716]

6 **Zong G**, Gao A, Hu FB, Sun Q. Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Meta-Analysis of Prospective Cohort Studies. *Circulation* 2016; **133**: 2370-2380 [PMID: 27297341 DOI: 10.1161/CIRCULATIONAHA.115.021101]

7 **John GK**, Wang L, Nanavati J, Twose C, Singh R, Mullin G. Dietary Alteration of the Gut Microbiome and Its Impact on Weight and Fat Mass: A Systematic Review and Meta-Analysis. *Genes (Basel)* 2018; 9 [PMID: 29547587 DOI: 10.3390/genes9030167]

8 **Valdes AM**, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. *BMJ* 2018; **361**: k2179 [PMID: 29899036 DOI: 10.1136/bmj.k2179]

9 **Walter J**, Martínez I, Rose DJ. Holobiont nutrition: considering the role of the gastrointestinal microbiota in the health benefits of whole grains. *Gut Microbes* 2013; **4**: 340-346 [PMID: 23645316 DOI: 10.4161/gmic.24707]

10 **Costabile A**, Klinder A, Fava F, Napolitano A, Fogliano V, Leonard C, Gibson GR, Tuohy KM. Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study. *Br J Nutr* 2008; **99**: 110-120 [PMID: 17761020 DOI: 10.1017/S0007114507793923]

11 **Martínez I**, Wallace G, Zhang C, Legge R, Benson AK, Carr TP, Moriyama EN, Walter J. Diet-induced metabolic improvements in a hamster model of hypercholesterolemia are strongly linked to alterations of the gut microbiota. *Appl Environ Microbiol* 2009; **75**: 4175-4184 [PMID: 19411417 DOI: 10.1128/AEM.00380-09]

12 **Vanegas SM**, Meydani M, Barnett JB, Goldin B, Kane A, Rasmussen H, Brown C, Vangay P, Knights D, Jonnalagadda S, Koecher K, Karl JP, Thomas M, Dolnikowski G, Li L, Saltzman E, Wu D, Meydani SN. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. *Am J Clin Nutr* 2017; **105**: 635-650 [PMID: 28179226 DOI: 10.3945/ajcn.116.146928]

13 **Ampatzoglou A**, Atwal KK, Maidens CM, Williams CL, Ross AB, Thielecke F, Jonnalagadda SS, Kennedy OB, Yaqoob P. Increased whole grain consumption does not affect blood biochemistry, body composition, or gut microbiology in healthy, low-habitual whole grain consumers. *J Nutr* 2015; **145**: 215-221 [PMID: 25644340 DOI: 10.3945/jn.114.202176]

14 **Lappi J**, Salojärvi J, Kolehmainen M, Mykkänen H, Poutanen K, de Vos WM, Salonen A. Intake of whole-grain and fiber-rich rye bread versus refined wheat bread does not differentiate intestinal microbiota composition in Finnish adults with metabolic syndrome. *J Nutr* 2013; **143**: 648-655 [PMID: 23514765 DOI: 10.3945/jn.112.172668]

15 **Langkamp-Henken B**, Nieves C, Culpepper T, Radford A, Girard SA, Hughes C, Christman MC, Mai V, Dahl WJ, Boileau T, Jonnalagadda SS, Thielecke F. Fecal lactic acid bacteria increased in adolescents randomized to whole-grain but not refined-grain foods, whereas inflammatory cytokine production decreased equally with both interventions. *J Nutr* 2012; **142**: 2025-2032 [PMID: 23014489 DOI: 10.3945/jn.112.164996]

16 **Vuholm S**, Nielsen DS, Iversen KN, Suhr J, Westermann P, Krych L, Andersen JR, Kristensen M. Whole-

Grain Rye and Wheat Affect Some Markers of Gut Health without Altering the Fecal Microbiota in Healthy Overweight Adults: A 6-Week Randomized Trial. *J Nutr* 2017; **147**: 2067-2075 [PMID: 28954842 DOI: 10.3945/jn.117.250647]

17 **Koecher KJ**, McKeown NM, Sawicki CM, Menon RS, Slavin JL. Effect of whole-grain consumption on changes in fecal microbiota: a review of human intervention trials. *Nutr Rev* 2019; **77**: 487-497 [PMID: 31086952 DOI: 10.1093/nutrit/nuz008]

18 **Sadeghi O**, Sadeghian M, Rahmani S, Maleki V, Larijani B, Esmaillzadeh A. Whole-Grain Consumption Does Not Affect Obesity Measures: An Updated Systematic Review and Meta-analysis of Randomized Clinical Trials. *Adv Nutr* 2019 [PMID: 31390462 DOI: 10.1093/advances/nmz076]

19 **Maki KC**, Palacios OM, Koecher K, Sawicki CM, Livingston KA, Bell M, Nelson Cortes H, McKeown NM. The Relationship between Whole Grain Intake and Body Weight: Results of Meta-Analyses of Observational Studies and Randomized Controlled Trials. *Nutrients* 2019; 11 [PMID: 31159235 DOI: 10.3390/nu11061245]

20 **Roager HM**, Vogt JK, Kristensen M, Hansen LBS, Ibrügger S, Mærkedahl RB, Bahl MI, Lind MV, Nielsen RL, Frøkiær H, Gøbel RJ, Landberg R, Ross AB, Brix S, Holck J, Meyer AS, Sparholt MH, Christensen AF, Carvalho V, Hartmann B, Holst JJ, Rumessen JJ, Linneberg A, Sicheritz-Pontén T, Dalgaard MD, Blennow A, Frandsen HL, Villas-Bôas S, Kristiansen K, Vestergaard H, Hansen T, Ekstrøm CT, Ritz C, Nielsen HB, Pedersen OB, Gupta R, Lauritzen L, Licht TR. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut* 2019; **68**: 83-93 [PMID: 29097438 DOI: 10.1136/gutjnl-2017-314786]

21 **Vetrani C**, Costabile G, Luongo D, Naviglio D, Rivellese AA, Riccardi G, Giacco R. Effects of whole-grain cereal foods on plasma short chain fatty acid concentrations in individuals with the metabolic syndrome. *Nutrition* 2016; **32**: 217-221 [PMID: 26706023 DOI: 10.1016/j.nut.2015.08.006]

22 **Alexander C**, Swanson KS, Fahey GC, Garleb KA. Perspective: Physiologic Importance of Short-Chain Fatty Acids from Nondigestible Carbohydrate Fermentation. *Adv Nutr* 2019; **10**: 576-589 [PMID: 31305907 DOI: 10.1093/advances/nmz004]

23 **Karl JP**, Saltzman E. The role of whole grains in body weight regulation. *Adv Nutr* 2012; **3**: 697-707 [PMID: 22983848 DOI: 10.3945/an.112.002782]

24 **Wanders AJ**, van den Borne JJ, de Graaf C, Hulshof T, Jonathan MC, Kristensen M, Mars M, Schols HA, Feskens EJ. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev* 2011; **12**: 724-739 [PMID: 21676152 DOI: 10.1111/j.1467-789X.2011.00895.x]

25 **Slavin J**, Green H. Dietary fibre and satiety. *Nutr Bull* 2007; **32**: 32-42 [DOI: 10.1111/j.1467-3010.2007.00603.x]

26 **Lee WJ**, Chen CY, Chong K, Lee YC, Chen SC, Lee SD. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. *Surg Obes Relat Dis* 2011; **7**: 683-690 [PMID: 21996600 DOI: 10.1016/j.soard.2011.07.009]

27 **Wang W**, Fann CSJ, Yang SH, Chen HH, Chen CY. Weight loss and metabolic improvements in obese patients undergoing gastric banding and gastric banded plication: A comparison. *Nutrition* 2019; **57**: 290-299 [PMID: 30219686 DOI: 10.1016/j.nut.2018.05.024]

28 **Maljaars PW**, Peters HP, Mela DJ, Masclee AA. Ileal brake: a sensible food target for appetite control. A review. *Physiol Behav* 2008; **95**: 271-281 [PMID: 18692080 DOI: 10.1016/j.physbeh.2008.07.018]

29 **Della Pepa G**, Vetrani C, Vitale M, Riccardi G. Wholegrain Intake and Risk of Type 2 Diabetes: Evidence from Epidemiological and Intervention Studies. *Nutrients* 2018; 10 [PMID: 30213062 DOI: 10.3390/nu10091288]

30 **Marventano S**, Vetrani C, Vitale M, Godos J, Riccardi G, Grosso G. Whole Grain Intake and Glycaemic Control in Healthy Subjects: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* 2017; 9 [PMID: 28753929 DOI: 10.3390/nu9070769]

31 **Huang HH**, Lee YC, Chen CY. Effects of burns on gut motor and mucosa functions. *Neuropeptides* 2018; **72**: 47-57 [PMID: 30269923 DOI: 10.1016/j.npep.2018.09.004]

32 **Suhr J**, Vuholm S, Iversen KN, Landberg R, Kristensen M. Wholegrain rye, but not wholegrain wheat, lowers body weight and fat mass compared with refined wheat: a 6-week randomized study. *Eur J Clin Nutr* 2017; **71**: 959-967 [PMID: 28327566 DOI: 10.1038/ejcn.2017.12]

33 **Karl JP**, Meydani M, Barnett JB, Vanegas SM, Goldin B, Kane A, Rasmussen H, Saltzman E, Vangay P, Knights D, Chen CO, Das SK, Jonnalagadda SS, Meydani SN, Roberts SB. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr* 2017; **105**: 589-599 [PMID: 28179223 DOI: 10.3945/ajcn.116.139683]

34 **Allegretti JR**, Kassam Z, Mullish BH, Chiang A, Carrellas M, Hurtado J, Marchesi JR, McDonald JAK, Pechlivanis A, Barker GF, Blanco JM, Garcia-Perez I, Wong WF, Gerardin Y, Silverstein M, Kennedy K, Thompson C. Effects of Fecal Microbiota Transplantation With Oral Capsules in Obese Patients. *Clin Gastroenterol Hepatol* 2019 [PMID: 31301451 DOI: 10.1016/j.cgh.2019.07.006]

35 **Fardet A**. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr Res Rev* 2010; **23**: 65-134 [PMID: 20565994 DOI: 10.1017/S0954422410000041]

36 **Cory H**, Passarelli S, Szeto J, Tamez M, Mattei J. The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. *Front Nutr* 2018; **5**: 87 [PMID: 30298133 DOI: 10.3389/fnut.2018.00087]

37 **Wang S**, Moustaid-Moussa N, Chen L, Mo H, Shastri A, Su R, Bapat P, Kwun I, Shen CL. Novel insights of dietary polyphenols and obesity. *J Nutr Biochem* 2014; **25**: 1-18 [PMID: 24314860 DOI: 10.1016/j.jnutbio.2013.09.001]

38 **Bertinato J**, Lavergne C, Rahimi S, Rachid H, Vu NA, Plouffe LJ, Swist E. Moderately Low Magnesium Intake Impairs Growth of Lean Body Mass in Obese-Prone and Obese-Resistant Rats Fed a High-Energy Diet. *Nutrients* 2016; 8 [PMID: 27136580 DOI: 10.3390/nu8050253]

39 **Moslehi N**, Vafa M, Sarrafzadeh J, Rahimi-Foroushani A. Does magnesium supplementation improve body composition and muscle strength in middle-aged overweight women? A double-blind, placebo-controlled, randomized clinical trial. *Biol Trace Elem Res* 2013; **153**: 111-118 [PMID: 23619906 DOI: 10.1007/s12011-013-9672-1]

40 **Rathnayake KM**, Silva K, Jayawardena R. Effects of zinc supplementation on obesity: study protocol for a randomized controlled clinical trial. *Trials* 2016; **17**: 534 [PMID: 27814737 DOI: 10.1186/s13063-016-1651-3]

41 **Mantzoros CS**, Prasad AS, Beck FW, Grabowski S, Kaplan J, Adair C, Brewer GJ. Zinc may regulate serum leptin concentrations in humans. *J Am Coll Nutr* 1998; **17**: 270-275 [PMID: 9627914 DOI:

10.1080/07315724.1998.10718758]
42 **Dørup I**, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. *Br J Nutr* 1991; **66**: 505-521 [PMID: 1772874 DOI: 10.1079/bjn19910051]
43 **Marlatt KL**, Ravussin E. Brown Adipose Tissue: an Update on Recent Findings. *Curr Obes Rep* 2017; **6**: 389-396 [PMID: 29101739 DOI: 10.1007/s13679-017-0283-6]
44 **Xiao X**, Bai J, Li MS, Zhang JY, Sun XJ, Dong Y. Supplementation of Fermented Barley Extracts with Lactobacillus Plantarum dy-1 Inhibits Obesity via a UCP1-dependent Mechanism. *Biomed Environ Sci* 2019; **32**: 578-591 [PMID: 31488234 DOI: 10.3967/bes2019.076]
45 **Izadi V**, Azadbakht L. Specific dietary patterns and concentrations of adiponectin. *J Res Med Sci* 2015; **20**: 178-184 [PMID: 25983773]
46 **Achari AE**, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int J Mol Sci* 2017; 18 [PMID: 28635626 DOI: 10.3390/ijms18061321]
47 **Qi Y**, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE, Ahima RS. Adiponectin acts in the brain to decrease body weight. *Nat Med* 2004; **10**: 524-529 [PMID: 15077108 DOI: 10.1038/nm1029]
48 **Huang HH**, Lee WJ, Chen SC, Chen TF, Lee SD, Chen CY. Bile acid and fibroblast growth factor 19 regulation in obese diabetes, and non-alcoholic fatty liver disease after sleeve gastrectomy. *J Clin Med* 2019; **8**: E815 [PMID: 31181641 DOI: 10.3390/jcm8060815]
49 **Wu WC**, Lee WJ, Yeh C, Chen SC, Chen CY. Do different bariatric surgery procedures impact hepassocin plasma levels in patients with type 2 diabetes mellitus? *Reports* 2019; **2**: 24 [DOI: 10.3390/reports204002]

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EDITORIAL

Epicardial adipose tissue deposition in patients with diabetes and renal impairment: Analysis of the literature

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Abstract

Diabetes mellitus (DM) is defined as a chronic disease of disordered metabolism with an ongoing increase in prevalence and incidence rates. Renal disease in patients with diabetes is associated with increased morbidity and premature mortality, particularly attributed to their very high cardiovascular risk. Since this group of patients frequently lacks specific symptomatology prior to the adverse events, a screening tool for the identification of high-risk patients is necessary. The epicardial adipose tissue (EAT) is a biologically active organ having properties similar to visceral adipose tissue and has been associated with metabolic diseases and coronary artery disease. Superior to conventional cardiovascular risk factors and anthropometric measures, including body mass index and waist circumference, the EAT can early predict the development of coronary artery disease. Assessment of EAT can be performed by two-dimensional echocardiography, magnetic resonance imaging or computer tomography. However, its role and significance in patients with DM and nephropathy has not been thoroughly evaluated. The aim of the current editorial is to evaluate all available evidence regarding EAT in patients with DM and renal impairment. Systematic search of the literature revealed that patients with DM and nephropathy have increased EAT measurements, uncontrolled underlying disease, high body mass index and raised cardiovascular risk markers. Acknowledging the practical implications of this test, EAT assessment could serve as a novel and non-invasive biomarker to identify high-risk patients for cardiovascular adverse events.

Key words: Epicardial adipose tissue; Epicardial fat; Diabetes mellitus; Renal impairment; Diabetic nephropathy; Cardiovascular risk

Core tip: The epicardial adipose tissue (EAT) is a biologically active organ and has been associated with metabolic diseases and coronary artery disease. EAT is a superior

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cardiovascular risk factor compared to conventional measures. This editorial evaluates the reported measurements of EAT in patients with diabetes mellitus and renal impairment, along with their clinical and laboratory characteristics. Patients with diabetes mellitus and nephropathy have increased EAT volume, uncontrolled disease, high body mass index and raised cardiovascular risk markers, when compared with healthy population. Based on current literature, EAT assessment could be used as a novel biomarker for the identification of patients at high risk for cardiovascular adverse events.

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INTRODUCTION

Diabetes mellitus (DM) consists a chronic multisystem disease of disordered metabolism with a worldwide prevalence reaching approximately 425 million[1]. The major complications of DM can be divided into macrovascular (cardiovascular disease) and microvascular [chronic kidney disease (CKD), diabetic retinopathy, diabetic neuropathy][2-4]. Diabetic nephropathy (DN) is a major cause of morbidity and mortality in diabetic patients, with a prevalence of 20%-40% in patients with type 1 or type 2 DM[5]. The majority of DM cases with CKD result from DN[6]. In addition, increased albuminuria and diminished renal function indicate unfavorable prognosis in terms of cardiovascular disease[7].

Epicardial adipose tissue (EAT) is a biologically active organ with properties similar to visceral adipose tissue[8,9]. EAT is defined as the adipose tissue located between the visceral pericardium and the myocardium, in the absence of a structure separating it from the myocardium and the epicardial vessels[8]. Assessment of EAT can be performed by the following imaging techniques: Two-dimensional echocardiography, magnetic resonance imaging (MRI), or computer tomography (CT)[10]. CT could concomitantly assess the presence of coronary calcification or stenosis[11]. Increased amounts of EAT have been associated with the presence of metabolic syndrome, DM and coronary artery disease[10]. EAT has also been proposed as a key mediator in the pathogenesis of cardiovascular disease in end-stage renal disease (ESRD) patients, the most common cause of death in this particular group[12,13].

THE NECESSITY OF A NEW SCREENING TOOL

EAT has been currently identified as a marker of cardiovascular risk[8,9]. Patients with DM and renal impairment have a high prevalence of cardiovascular adverse events, frequently lacking warning symptoms such as chest pain, usually due to either diabetic autonomic neuropathy, uremic neuropathy, or impaired exercise capacity[14,15]. This high-risk group of patients requires regular follow-up, since cardiovascular disease consists the single leading cause of morbidity and mortality in patients with CKD in all stages[6]. In light of these considerations, this editorial will focus on the value of EAT assessment in patients with DM and renal disease.

AVAILABLE EVIDENCE

Two online databases (PubMed and Scopus) were systematically searched for articles published from inception up to December 2019. The search term applied consisted of the following key words: ("diabetes mellitus" OR "diabetic" OR "diabetes") AND ("epicardial fat" OR "epicardial adipose" OR "subepicardial fat" OR "subepicardial adipose"), in order to identify all published articles reporting data on patients with DM and renal impairment who were assessed for EAT measurements. Reference lists of full articles were also reviewed.

Articles with the following requirements were included: (1) Primary research papers (*e.g.*, case reports, case series, observational studies, randomized control trials);

(2) Studies describing patients (adults ≥ 18 years) with type 1 or type 2 DM and renal impairment who had undergone measurement of EAT deposition; and (3) Studies published in English.

Studies containing at least one of the following items were excluded: (1) Studies published in other than English language; (2) Experimental studies on animals; (3) Cases not diagnosed with DM; (4) Studies including exclusively patients with gestational DM; (5) Secondary research papers; (6) Editorials and papers not reporting results of primary research; and (7) Studies not referring to patients with DM, renal impairment and epicardial fat deposition measurements.

Study outcomes were to evaluate all available evidence regarding EAT measurements in patients with DM and renal impairment; to record all clinical and laboratory characteristics and comorbid conditions; and to identify possible risk factors that could contribute to epicardial fat tissue deposition in these patients.

ANALYSIS OF CURRENT LITERATURE

A total of eight studies referring to patients with DM and renal impairment with EAT assessment were incorporated in the analysis[16-22]. Table 1 summarizes the characteristics of the 8 included studies and the 452 patients that were analyzed. All were cross-sectional, except one case-report. According to data available in 368 patients, mean age was 59 years of age (range: 49-71) and 140 (31%) patients were female[16,17,19,21,23].

Epicardial adipose tissue characteristics

The EAT was quantified in all eight studies. Investigators used either transthoracic echocardiography[16,17] or multi-detector CT (MDCT)[18-22] to assess epicardial fat. Transthoracic echocardiography was used to measure EAT thickness in three studies: mean 3.2 ± 1.6 mm[17], median 4.5 mm (range: 2-9 mm) and 5.3 mm (range: 4.4-9 mm) in the micro- and macro-albuminuric group respectively[16], and mean 6.5 ± 1.4 mm[23]. According to previous studies, the mean thickness value in systole described by Iacobellis *et al*[24] during the investigation of cardiovascular risk, was 6.8 mm (range: 1.1-22.6). The mean value in diastole introduced by Jeong *et al*[25] in more than 200 patients admitted for coronary angiography, was 6.4 mm (range: 1.1-16.6). Although there is no consensus for EAT thickness cut-off values, measurements higher than 5 mm indicate increased EAT, especially in low risk populations[8].

MDCT was used to assess EAT volume in cm^3 or mm^3 units. In one study, EAT was expressed as single slice epicardial fat volume or as single slice epicardial fat area[20]. A previous study determined that single slice epicardial fat area measured at the level of left main coronary artery provides a reliable estimate of total epicardial fat volume[26]. Most of the studies using MDCT included the range of -190 to -30 of Hounsfield units regarding determination of fat. The mean EAT volume of the four studies was 258.4 cm^3 (range: 0.01-487)[18-20,22]. One study reported the median EAT volume of 17 patients which equaled 215.5 cm^3 (range: 126.5-271.2)[21]. The value of 0.01 cm^3, reported in one study, could be attributed to the different range of Hounsfield units used for determination of fat density[18]. In comparison, the mean volume of EAT ranged from 68 ± 34 cm^3 to 124 ± 50 cm^3 in previous population-based studies[27,28]. A cohort study derived from Framingham Heart Study, found a mean EAT volume of 110 ± 41 cm^3 in women and 137 ± 53 cm^3 in men[11]. Based on current literature, a cut-off EAT volume of more than 125 cm^3 can be considered as abnormal[8]. Hence, patients with DM and renal impairment seem to have an increased EAT volume compared to healthy populations.

Diabetes mellitus characteristics

Type of DM was reported in 359 patients[16-18], of which 350 (96.8%) had type 2 DM[16,17,23] and 9 (3.2%) had type 1 DM[18]. Duration of DM was reported in 350 patients and ranged from 0 to 30 years[16,17,23]. The HbA1c levels, reported in 350 patients, ranged from 6% to 14.5%, with an approximate mean value of 8.7%[16,17,23]. Among 291 patients with available data on treatment of diabetes, 223 (76.6%) patients were being treated with oral antidiabetics and/or 180 (80.7%) patients were being treated with either insulin injections or insulin infusion pump[16,17,23]. Average body mass index (BMI), estimated in 368 patients, was 32.3 kg/m^2 (range: 28.5-34.4)[16,17,19,21,23]. The characteristics of DM are reported in Table 2.

BMI is an anthropometric measure widely used to assess visceral adipose tissue deposition[29]. Excess visceral adipose tissue is a marker of patients with high risk for cardiovascular disease[30,31]. This finding is in line with the current literature suggesting that visceral adipose tissue has a strong correlation with EAT[30,32].

Table 1 Study and patient characteristics

Ref.	Study design	Age group	Number of patients with diabetes and renal impairment	Age, mean in years (range)	Gender, female, *n* (%)
Akbas *et al*[16], 2014, Turkey	Cross-sectional	Adults	68	Micro-albuminuric patients: 60 ± 11 Macro-albuminuric patients: 59 ± 9.6	34 (50)
Christensen *et al*[17], 2017, Denmark	Cross-sectional	Adults	200	59 (50-68)	48 (24)
Darabian *et al*[18], 2016, United States	Cross-sectional	Adults	9	NR	NR
Do *et al*[19], 2009, Korea	Case-report	Adult	1	59	1 (100)
Kerr *et al*[20], 2013, Canada	Cross-sectional	Adults	36	NR	NR
Tonbul *et al*[21], 2011, Turkey	Cross-sectional	Adults	17	58 (45-71)	8 (47)
Turan *et al*[22], 2013, Turkey	Cross-sectional	Adults	39	NR	NR
Turan *et al*[23], 2019, Turkey	Cross-sectional	Adults	82	59.4 ± 7.6	49 (59.7)

NR: Not reported.

Renal impairment characteristics

Patients from all different CKD stages were included. Albuminuria was used as an early and sensitive marker of renal impairment in three studies[16,17,23]. One study included patients with both macroalbuminuria and ESRD[18]. Albuminuria was estimated in 350 patients[16,17,23], among which 274 patients had microalbuminuria (30-299 mg/g Cr) and 76 patients had macroalbuminuria (> 300 mg/g Cr)[16,17,23]. Three studies revealed that albuminuria was a significant predictor of greater EAT[16,18,20]. Mean eGFR and mean creatinine, assessed in 350 patients, were 82 mL/min/1.73/m^2 (range: 20-123)[16,17,23] and 1.0 mg/dL (range: 0.4-3.5), respectively[16,17,23]. Patients with ESRD were reported in 57 patients in three studies[19,21,22]. Renal impairment characteristics are depicted in Table 2.

Albuminuria is a marker of diffuse endothelial dysfunction associated with hypertension, smoking, DM, obesity and dyslipidemia[33,34]. Albuminuria consists a risk factor for cardiovascular disease and is associated with increased abdominal adiposity[35]. The ADVANCE Study showed that albuminuria and reduced GFR were independently and additively associated with increased cardiovascular and renal events in patients with type 2 DM[36].

EAT is a biologically active organ having properties similar to the visceral adipose tissue, secreting proatherogenic hormones and cytokines such as leptin and resistin[8]. The absence of a specific fascial layer or aponeurosis between the epicardial vessels and the myocardium surrounding the adventitia of coronary arteries and their branches, allows for a shared micro-circulation and the subsequent development of coronary artery disease[8,37]. The protective effect of adiponectin which acts by increasing insulin sensitivity is found to be reduced in patients with increased deposits of EAT[38,39]. CKD involves chronic inflammation, characterized by the presence of increased inflammatory markers, including C-reactive protein, IL-6, and TNF-α[12]. C-reactive protein is also associated with the prevalence of metabolic syndrome, hypertension and DM in United States adults[40]. Atherosclerosis is greatly enhanced under higher inflammation status or increased oxidative stress[12]. Microvascular complications of DM, including DN, are promoted under the influence of inflammation and oxidative stress by the metabolism of hyperglycemia and dyslipidemia[16,41-46].

Conclusively, the presence of albuminuria along with endothelial dysfunction and increased abdominal adiposity, the secretion of proatherogenic hormones and cytokines by EAT in combination with the loss of protective effect of adiponectin, the pronounced inflammation and oxidative stress in CKD patients, all contribute to the development of coronary artery disease in patients with DM and renal impairment.

Coronary artery calcium score

Total coronary artery calcium score (CACS) was evaluated in 217 patients[17,21]. Left

Table 2 Diabetes and renal disease characteristics

Ref. (number of patients)	Diabetes type	Diabetes duration, median (IQR) or mean ± SD in years	Criteria for renal impairment diagnosis	eGFR,mean ± SD (mL/min/1.73 m^2)	Albuminuria, median (IQR) (units)	Creatinine, median (IQR) or mean ± SD (mg/dL)	Other related measurements
Akbas *et al*[16] (*n* = 68)	Type 2	Micro-albuminuric patients: 9 (0-30); Macro-albuminuric patients: 8.5 (1-29)	Presence of albuminuria (> 30 mg/g Cr)	Micro-albuminuric patients: 94 ± 29; Macro-albuminuric patients: 64 ± 44	Micro-albuminuric patients: 74 (33-294) (mg/g Cr); Macro-albuminuric patients: 716 (312-1985) (mg/g Cr)	Micro-albuminuric patients: 0.75 (0.5-2); Macro-albuminuric patients: 1.4 (0.4-3.5)	BMI (kg/m^2): 30; Waist circumference (cm): 102; SBP (mmHg): 135 (90-210); DBP (mmHg): 78 (40-110)
Christensen *et al*[17] (*n* = 200)	Type 2	13 ± 7	Presence of albuminuria (> 30 mg/g Cr)	89 ± 17	102 (39-229) (mg/24 h)	0.86 ± 0.2	BMI (kg/m^2): 32.6; SBP (mmHg): 130 ± 16; Cholesterol (mg/dL): 151; LDL (mg/dL): 73.4; HDL (mg/dL): 46.4
Darabian *et al*[18] (*n* = 9)	Type 1	NR	Presence of albuminuria (> 30 mg/g Cr) or ESRD	NR	NR	NR	NR
Do *et al*[19] (*n* = 1)	NR	NR	ESRD (peritoneal dialysis)	(End-stage renal failure)	NR	9.13	BMI (kg/m^2): 29.6
Kerr *et al*[20] (*n* = 36)	NR	NR	CKD diagnosis according to National Kidney Foundation Criteria	NR	NR	NR	NR
Tonbul *et al*[21] (*n* = 17)	NR	NR	ESRD (hemodialysis or peritoneal dialysis)	(End-stage renal failure)	NR	NR	BMI (kg/m^2): 28.5; SBP (mmHg): 135 ± 27; DBP (mmHg): 80 ± 16; LDL (mg/dL): 120; HDL (mg/dL): 37; Triglycerides (mg/dL): 127
Turan *et al*[22] (*n* = 39)	NR	NR	ESRD (hemodialysis)	(End-stage renal failure)	NR	NR	NR
Turan *et al*[23] (*n* = 82)	Type 2	12.7 ± 6.7	Presence of micro-albuminuria (30-300 mg/g)	80 ± 20	134 ± 83 (mg/g)	0.91 ± 0.2	BMI (kg/m^2): 34.4 ± 6.2; SBP (mmHg): 135 ± 16; DBP (mmHg): 80.5 ± 11; LDL (mg/dL): 123 ± 35; HDL (mg/dL): 44 ± 10.6; Triglycerides (mg/dL): 211

BMI: Body mass index; CKD: Chronic kidney disease; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; HDL: High density lipoprotein; IQR: Interquartile range; LDL: Low density lipoprotein; NR: Not reported; SD: Standard deviation; SBP: Systolic blood pressure.

anterior descending coronary artery, circumflex coronary artery and right coronary artery were added to calculate the CACS according to the protocol by Agatston *et al*[47], for quantification of CACS using ultrafast CT. The mean CACS was 192.5, with a normal range between 1 and 10.

CACS is an index that assesses the severity of atherosclerotic vascular disease and predicts the risk of future adverse cardiovascular events[48]. CACS equal to 192.5 is classified as moderate risk (relative risk: 4.3) of having a cardiovascular event according to Agatston *et al*[47]. According to previous studies, individuals with DN had a significantly higher prevalence and severity of CACS score when compared to normoalbuminuric diabetic patients[49]. Also, the progression of CACS in patients with

DM and CKD is more prevalent in those with albuminuria when compared with normoalbuminuric patient controls[50]. Increased EAT volume was also correlated with CACS in ESRD patients[21]. Two studies included measurements of inflammatory markers[16,17], which were found to be associated with increased albuminuria[16] and with EAT[17,51]. Based on the aforementioned results and according to the literature, EAT volume is associated with the malnutrition, inflammation and atherosclerosis/calcification syndrome in ESRD patients, which is associated with increased morbidity and mortality.

CRITICAL APPRAISAL OF THE LITERATURE

The above findings should be considered in relation to the fact that most available evidence is derived from observational cross-sectional studies with relatively small sample sizes. Several determinants of EAT including obesity, age and ethnicity, which may set different normal ranges, were not reported in all patients[24,52-56]. Additionally, several characteristics of DM and renal disease were not reported in all patients. MDCT protocol and definitions used varied among studies. Although MRI is considered the standard of reference for EAT quantification[57], no studies that utilized MRI were available.

FUTURE DIRECTIONS

According to current literature, EAT can be supported as a superior cardiovascular risk factor compared to conventional anthropometric measures, indicating that localized fat depositions predict more accurately the future adverse coronary events[10]. EAT was particularly increased in non-calcified and mixed plaques, the most commonly implicated in cardiovascular events, in comparison with purely calcified plaques[53,58]. At this point, there is evident need to establish cut-off points for EAT volume and thickness in high-risk patient groups such as patients with DM and DN; to that end, future studies should prefer to opt for EAT volume over thickness assessment, using standardized MDCT or MRI protocols. In addition, future studies should report more detailed data on patients, including DM and DN characteristics and somatometric data. Although not within the scope of the current review, studies have also focused on the reduction of EAT through conservative, pharmacological or surgical means, yielding various results[9,59-65]. Future studies should assess the safety and long-term effects of EAT reduction. This way, EAT could concomitantly be used as a screening tool and as a follow-up marker.

CONCLUSION

Available evidence shows that patients with DM and renal impairment have uncontrolled disease, with raised cardiovascular risk markers, high BMI and increased EAT measurements, when compared with healthy populations. Although specific cut-off limits need to be developed and acknowledging the practical issues concerning this test, EAT assessment could be used as a novel practical and inexpensive biomarker for identification of patients at high risk for cardiovascular adverse events.

REFERENCES

1 **IDF Diabetes Atlas**. IDF diabetes atlas 8th edition [Internet]. 2017 [cited 2019 May 13]. Available from: https://www.diabetesatlas.org/

2 **Donaghue KC**, Marcovecchio ML, Wadwa RP, Chew EY, Wong TY, Calliari LE, Zabeen B, Salem MA, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes* 2018; **19** Suppl 27: 262-274 [PMID: 30079595 DOI: 10.1111/pedi.12742]

3 **Papatheodorou K**, Papanas N, Banach M, Papazoglou D, Edmonds M. Complications of Diabetes 2016. *J Diabetes Res* 2016; **2016**: 6989453 [PMID: 27822482 DOI: 10.1155/2016/6989453]

4 **Papatheodorou K**, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. *J Diabetes Res* 2018; **2018**: 3086167 [PMID: 29713648 DOI: 10.1155/2018/3086167]

5 **Rossing P**, Persson F, Frimodt-Møller M. Prognosis and treatment of diabetic nephropathy: Recent advances and perspectives. *Nephrol Ther* 2018; **14** Suppl 1: S31-S37 [PMID: 29606261 DOI: 10.1016/j.nephro.2018.02.007]

6 **Persson F**, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. *Kidney Int Suppl (2011)* 2018; **8**: 2-7 [PMID: 30675433 DOI: 10.1016/j.kisu.2017.10.003]

7 **Levey AS**, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011; **80**: 17-28 [PMID: 21150873 DOI: 10.1038/ki.2010.483]

8 **Bertaso AG**, Bertol D, Duncan BB, Foppa M. Epicardial fat: definition, measurements and systematic review of main outcomes. *Arq Bras Cardiol* 2013; **101**: e18-e28 [PMID: 23917514 DOI: 10.5935/abc.20130138]

9 **Katsiki N**, Mikhailidis DP, Wierzbicki AS. Epicardial fat and vascular risk: a narrative review. *Curr Opin Cardiol* 2013; **28**: 458-463 [PMID: 23591557 DOI: 10.1097/HCO.0b013e3283605fba]

10 **Talman AH**, Psaltis PJ, Cameron JD, Meredith IT, Seneviratne SK, Wong DT. Epicardial adipose tissue: far more than a fat depot. *Cardiovasc Diagn Ther* 2014; **4**: 416-429 [PMID: 25610800 DOI: 10.3978/j.issn.2223-3652.2014.11.05]

11 **Rosito GA**, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, O'Donnell CJ, Fox CS. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008; **117**: 605-613 [PMID: 18212276 DOI: 10.1161/CIRCULATIONAHA.107.743062]

12 **Graham-Brown MP**, McCann GP, Burton JO. Epicardial adipose tissue in patients with end-stage renal disease on haemodialysis. *Curr Opin Nephrol Hypertens* 2015; **24**: 517-524 [PMID: 26335554 DOI: 10.1097/MNH.0000000000000161]

13 **Russo R**, Di Iorio B, Di Lullo L, Russo D. Epicardial adipose tissue: new parameter for cardiovascular risk assessment in high risk populations. *J Nephrol* 2018; **31**: 847-853 [PMID: 29704210 DOI: 10.1007/s40620-018-0491-5]

14 **Hakeem A**, Bhatti S, Chang SM. Screening and risk stratification of coronary artery disease in end-stage renal disease. *JACC Cardiovasc Imaging* 2014; **7**: 715-728 [PMID: 25034921 DOI: 10.1016/j.jcmg.2013.12.015]

15 **Bravo PE**, Psaty BM, Di Carli MF, Branch KR. Identification of coronary heart disease in asymptomatic individuals with diabetes mellitus: to screen or not to screen. *Colomb Med (Cali)* 2015; **46**: 41-46 [PMID: 26019384 DOI: 10.25100/cm.v46i1.1895]

16 **Akbas EM**, Demirtas L, Ozcicek A, Timuroglu A, Bakirci EM, Hamur H, Ozcicek F, Turkmen K. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. *Int J Clin Exp Med* 2014; **7**: 1794-1801 [PMID: 25126182]

17 **Christensen RH**, von Scholten BJ, Hansen CS, Heywood SE, Rosenmeier JB, Andersen UB, Hovind P, Reinhard H, Parving HH, Pedersen BK, Jørgensen ME, Jacobsen PK, Rossing P. Epicardial, pericardial and total cardiac fat and cardiovascular disease in type 2 diabetic patients with elevated urinary albumin excretion rate. *Eur J Prev Cardiol* 2017; **24**: 1517-1524 [PMID: 28650207 DOI: 10.1177/2047487317717820]

18 **Darabian S**, Backlund JY, Cleary PA, Sheidaee N, Bebu I, Lachin JM, Budoff MJ; DCCT/EDIC Research Group. Significance of Epicardial and Intrathoracic Adipose Tissue Volume among Type 1 Diabetes Patients in the DCCT/EDIC: A Pilot Study. *PLoS One* 2016; **11**: e0159958 [PMID: 27459689 DOI: 10.1371/journal.pone.0159958]

19 **Do GW**, Ku BS, Park CS, Kim SJ, Shin ES, Choi SH, Lee SG. A case of constrictive pericarditis associated with huge epicardial fat volume. *Korean Circ J* 2009; **39**: 116-120 [PMID: 19949598 DOI: 10.4070/kcj.2009.39.3.116]

20 **Kerr JD**, Holden RM, Morton AR, Nolan RL, Hopman WM, Pruss CM, Garland JS. Associations of epicardial fat with coronary calcification, insulin resistance, inflammation, and fibroblast growth factor-23 in stage 3-5 chronic kidney disease. *BMC Nephrol* 2013; **14**: 26 [PMID: 23351146 DOI: 10.1186/1471-2369-14-26]

21 **Tonbul HZ**, Turkmen K, Kayıkcıoglu H, Ozbek O, Kayrak M, Biyik Z. Epicardial adipose tissue and coronary artery calcification in diabetic and nondiabetic end-stage renal disease patients. *Ren Fail* 2011; **33**: 770-775 [PMID: 21770856 DOI: 10.3109/0886022X.2011.599913]

22 **Turan MN**, Gungor O, Asci G, Kircelli F, Acar T, Yaprak M, Ceylan N, Demirci MS, Bayraktaroglu S, Toz H, Ozkahya M, Ok E. Epicardial adipose tissue volume and cardiovascular disease in hemodialysis patients. *Atherosclerosis* 2013; **226**: 129-133 [PMID: 23159099 DOI: 10.1016/j.atherosclerosis.2012.10.061]

23 **Turan Y**, Turan E. Aortic Stiffness Index And Carotid Intima-Media Thickness Are Independently Associated With The Presence Of Microalbuminuria In Patients With Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes* 2019; **12**: 1889-1896 [PMID: 31571963 DOI: 10.2147/DMSO.S223880]

24 **Iacobellis G**, Willens HJ, Barbaro G, Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. *Obesity (Silver Spring)* 2008; **16**: 887-892 [PMID: 18379565 DOI: 10.1038/oby.2008.6]

25 **Jeong JW**, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, Rhee SJ, Lee EM, Lee J, Yoo NJ, Kim NH, Park JC. Echocardiographic epicardial fat thickness and coronary artery disease. *Circ J* 2007; **71**: 536-539 [PMID: 17384455 DOI: 10.1253/circj.71.536]

26 **Oyama N**, Goto D, Ito YM, Ishimori N, Mimura R, Furumoto T, Kato F, Tsutsui H, Tamaki N, Terae S, Shirato H. Single-slice epicardial fat area measurement: do we need to measure the total epicardial fat volume? *Jpn J Radiol* 2011; **29**: 104-109 [PMID: 21359935 DOI: 10.1007/s11604-010-0524-z]

27 **Mahabadi AA**, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, O'Donnell CJ, Fox CS, Hoffmann U. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J* 2009; **30**: 850-856 [PMID: 19136488 DOI: 10.1093/eurheartj/ehn573]

28 **Ding J**, Kritchevsky SB, Hsu FC, Harris TB, Burke GL, Detrano RC, Szklo M, Criqui MH, Allison M, Ouyang P, Brown ER, Carr JJ. Association between non-subcutaneous adiposity and calcified coronary plaque: a substudy of the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr* 2008; **88**: 645-650 [PMID: 18779279 DOI: 10.1093/ajcn/88.3.645]

29 **Kannel WB**, Cupples LA, Ramaswami R, Stokes J, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. *J Clin Epidemiol* 1991; **44**: 183-190 [PMID: 1995775 DOI: 10.1016/0895-4356(91)90265-b]

30 **De Larochellière E**, Côté J, Gilbert G, Bibeau K, Ross MK, Dion-Roy V, Pibarot P, Després JP, Larose E. Visceral/epicardial adiposity in nonobese and apparently healthy young adults: association with the cardiometabolic profile. *Atherosclerosis* 2014; **234**: 23-29 [PMID: 24589564 DOI: 10.1016/j.atherosclerosis.2014.01.053]

31 **Katsiki N**, Athyros VG, Mikhailidis DP. Abnormal Peri-Organ or Intra-organ Fat (APIFat) Deposition: An Underestimated Predictor of Vascular Risk? *Curr Vasc Pharmacol* 2016; **14**: 432-441 [PMID: 27456108 DOI: 10.2174/1570161114666160722112738]

32 **Karayiannakis AJ**, Makri GG, Mantzioka A, Karousos D, Karatzas G. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg* 1997; **84**: 467-471 [PMID: 9112894 DOI: 10.1002/bjs.1800840411]

33 **Karagiannis A**, Mikhailidis DP, Tziomalos K, Kakafika AI, Athyros VG. Has the time come for a new definition of microalbuminuria? *Curr Vasc Pharmacol* 2008; **6**: 81-83 [PMID: 18393908 DOI: 10.2174/157016108783955329]

34 **Futrakul N**, Sridama V, Futrakul P. Microalbuminuria--a biomarker of renal microvascular disease. *Ren Fail* 2009; **31**: 140-143 [PMID: 19212911 DOI: 10.1080/08860220802595948]

35 **Tamba S**, Nakatsuji H, Kishida K, Noguchi M, Ogawa T, Okauchi Y, Nishizawa H, Imagawa A, Nakamura T, Matsuzawa Y, Funahashi T, Shimomura I. Relationship between visceral fat accumulation and urinary albumin-creatinine ratio in middle-aged Japanese men. *Atherosclerosis* 2010; **211**: 601-605 [PMID: 20363472 DOI: 10.1016/j.atherosclerosis.2010.02.037]

36 **Rifkin DE**, Katz R, Chonchol M, Fried LF, Cao J, de Boer IH, Siscovick DS, Shlipak MG, Sarnak MJ. Albuminuria, impaired kidney function and cardiovascular outcomes or mortality in the elderly. *Nephrol Dial Transplant* 2010; **25**: 1560-1567 [PMID: 20008829 DOI: 10.1093/ndt/gfp646]

37 **Company JM**, Booth FW, Laughlin MH, Arce-Esquivel AA, Sacks HS, Bahouth SW, Fain JN. Epicardial fat gene expression after aerobic exercise training in pigs with coronary atherosclerosis: relationship to visceral and subcutaneous fat. *J Appl Physiol (1985)* 2010; **109**: 1904-1912 [PMID: 20947714 DOI: 10.1152/japplphysiol.00621.2010]

38 **Jain SH**, Massaro JM, Hoffmann U, Rosito GA, Vasan RS, Raji A, O'Donnell CJ, Meigs JB, Fox CS. Cross-sectional associations between abdominal and thoracic adipose tissue compartments and adiponectin and resistin in the Framingham Heart Study. *Diabetes Care* 2009; **32**: 903-908 [PMID: 19223612 DOI: 10.2337/dc08-1733]

39 **Katsiki N**, Mantzoros C, Mikhailidis DP. Adiponectin, lipids and atherosclerosis. *Curr Opin Lipidol* 2017; **28**: 347-354 [PMID: 28463859 DOI: 10.1097/MOL.0000000000000431]

40 **Mazidi M**, Toth PP, Banach M. C-reactive Protein Is Associated With Prevalence of the Metabolic Syndrome, Hypertension, and Diabetes Mellitus in US Adults. *Angiology* 2018; **69**: 438-442 [PMID: 28914081 DOI: 10.1177/0003319717729288]

41 **Goldberg RB**. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab* 2009; **94**: 3171-3182 [PMID: 19509100 DOI: 10.1210/jc.2008-2534]

42 **Lim AK**, Tesch GH. Inflammation in diabetic nephropathy. *Mediators Inflamm* 2012; **2012**: 146154 [PMID: 22969168 DOI: 10.1155/2012/146154]

43 **Astrup AS**, Tarnow L, Pietraszek L, Schalkwijk CG, Stehouwer CD, Parving HH, Rossing P. Markers of endothelial dysfunction and inflammation in type 1 diabetic patients with or without diabetic nephropathy followed for 10 years: association with mortality and decline of glomerular filtration rate. *Diabetes Care* 2008; **31**: 1170-1176 [PMID: 18332153 DOI: 10.2337/dc07-1960]

44 **Sun YM**, Su Y, Li J, Wang LF. Recent advances in understanding the biochemical and molecular mechanism of diabetic nephropathy. *Biochem Biophys Res Commun* 2013; **433**: 359-361 [PMID: 23541575 DOI: 10.1016/j.bbrc.2013.02.120]

45 **Mima A**. Inflammation and oxidative stress in diabetic nephropathy: new insights on its inhibition as new therapeutic targets. *J Diabetes Res* 2013; **2013**: 248563 [PMID: 23862164 DOI: 10.1155/2013/248563]

46 **Luis-Rodríguez D**, Martínez-Castelao A, Górriz JL, De-Álvaro F, Navarro-González JF. Pathophysiological role and therapeutic implications of inflammation in diabetic nephropathy. *World J Diabetes* 2012; **3**: 7-18 [PMID: 22253941 DOI: 10.4239/wjd.v3.i1.7]

47 **Agatston AS**, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15**: 827-832 [PMID: 2407762 DOI: 10.1016/0735-1097(90)90282-t]

48 **Neves PO**, Andrade J, Monção H. Coronary artery calcium score: current status. *Radiol Bras* 2017; **50**: 182-189 [PMID: 28670030 DOI: 10.1590/0100-3984.2015.0235]

49 **Mehrotra R**, Budoff M, Christenson P, Ipp E, Takasu J, Gupta A, Norris K, Adler S. Determinants of coronary artery calcification in diabetics with and without nephropathy. *Kidney Int* 2004; **66**: 2022-2031 [PMID: 15496175 DOI: 10.1111/j.1523-1755.2004.00974.x]

50 **Mehrotra R**, Budoff M, Hokanson JE, Ipp E, Takasu J, Adler S. Progression of coronary artery calcification in diabetics with and without chronic kidney disease. *Kidney Int* 2005; **68**: 1258-1266 [PMID: 16105059 DOI: 10.1111/j.1523-1755.2005.00522.x]

51 **Gerszten RE**, Garcia-Zepeda EA, Lim YC, Yoshida M, Ding HA, Gimbrone MA, Luster AD, Luscinskas FW, Rosenzweig A. MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. *Nature* 1999; **398**: 718-723 [PMID: 10227295 DOI: 10.1038/19546]

52 **Iacobellis G**, Singh N, Wharton S, Sharma AM. Substantial changes in epicardial fat thickness after weight loss in severely obese subjects. *Obesity (Silver Spring)* 2008; **16**: 1693-1697 [PMID: 18451775 DOI: 10.1038/oby.2008.251]

53 **Alexopoulos N**, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010; **210**: 150-154 [PMID: 20031133 DOI: 10.1016/j.atherosclerosis.2009.11.020]

54 **Silaghi A**, Piercecchi-Marti MD, Grino M, Leonetti G, Alessi MC, Clement K, Dadoun F, Dutour A. Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy. *Obesity (Silver Spring)* 2008; **16**: 2424-2430 [PMID: 18719675 DOI: 10.1038/oby.2008.379]

55 **Katsiki N**, Mikhailidis DP. Epicardial fat: a novel marker of subclinical atherosclerosis in clinical practice? *Anatol J Cardiol* 2017; **17**: 64-65 [PMID: 28144006 DOI: 10.14744/AnatolJCardiol.2017.22129]

56 **Duncan BB**, Chambless LE, Schmidt MI, Szklo M, Folsom AR, Carpenter MA, Crouse JR. Correlates of body fat distribution. Variation across categories of race, sex, and body mass in the atherosclerosis risk in communities study. The Atherosclerosis Risk in communities (ARIC) Study Investigators. *Ann Epidemiol* 1995; **5**: 192-200 [PMID: 7606308 DOI: 10.1016/1047-2797(94)00106-4]

57 **Iacobellis G**, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *J Clin Endocrinol Metab* 2003; **88**: 5163-5168 [PMID: 14602744 DOI: 10.1210/jc.2003-030698]

58 **Blankstein R**, Ferencik M. The vulnerable plaque: Can it be detected with Cardiac CT? *Atherosclerosis* 2010; **211**: 386-389 [PMID: 20619414 DOI: 10.1016/j.atherosclerosis.2010.06.014]

59 **Athyros VG**, Katsiki N, Karagiannis A, Mikhailidis DP. Statins can improve proteinuria and glomerular filtration rate loss in chronic kidney disease patients, further reducing cardiovascular risk. Fact or fiction? *Expert Opin Pharmacother* 2015; **16**: 1449-1461 [PMID: 26037614 DOI: 10.1517/14656566.2015.1053464]

60 **Gaborit B**, Jacquier A, Kober F, Abdesselam I, Cuisset T, Boullu-Ciocca S, Emungania O, Alessi MC, Clément K, Bernard M, Dutour A. Effects of bariatric surgery on cardiac ectopic fat: lesser decrease in epicardial fat compared to visceral fat loss and no change in myocardial triglyceride content. *J Am Coll Cardiol* 2012; **60**: 1381-1389 [PMID: 22939560 DOI: 10.1016/j.jacc.2012.06.016]

61 **Liang KW**, Tsai IC, Lee WJ, Lin SY, Lee WL, Lee IT, Fu CP, Wang JS, Sheu WH. Correlation between reduction of superior interventricular groove epicardial fat thickness and improvement of insulin resistance after weight loss in obese men. *Diabetol Metab Syndr* 2014; **6**: 115 [PMID: 25383099 DOI: 10.1186/1758-5996-6-115]

62 **Parisi V**, Petraglia L, D'Esposito V, Cabaro S, Rengo G, Caruso A, Grimaldi MG, Baldascino F, De Bellis A, Vitale D, Formisano R, Ferro A, Paolillo S, Davin L, Lancellotti P, Formisano P, Perrone Filardi P, Ferrara N, Leosco D. Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue. *Int J Cardiol* 2019; **274**: 326-330 [PMID: 30454723 DOI: 10.1016/j.ijcard.2018.06.106]

63 **Díaz-Rodríguez E**, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR, Eiras S. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res* 2018; **114**: 336-346 [PMID: 29016744 DOI: 10.1093/cvr/cvx186]

64 **Sacks HS**, Fain JN, Cheema P, Bahouth SW, Garrett E, Wolf RY, Wolford D, Samaha J. Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone. *Diabetes Care* 2011; **34**: 730-733 [PMID: 21289232 DOI: 10.2337/dc10-2083]

65 **Grosso AF**, de Oliveira SF, Higuchi Mde L, Favarato D, Dallan LA, da Luz PL. Synergistic anti-inflammatory effect: simvastatin and pioglitazone reduce inflammatory markers of plasma and epicardial adipose tissue of coronary patients with metabolic syndrome. *Diabetol Metab Syndr* 2014; **6**: 47 [PMID: 24684779 DOI: 10.1186/1758-5996-6-47]

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ORIGINAL ARTICLE

Case Control Study

Wrist circumference: A new marker for insulin resistance in African women with polycystic ovary syndrome

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Abstract

BACKGROUND

Insulin resistance (IR) is the main complication found in 35%-80% of women with polycystic ovary syndrome (PCOS). However, there is no definite consensus regarding which marker to use for its assessment in PCOS women. Research has shown that hyperinsulinemia is correlated with increased bone mass. Given that most women with PCOS are insulin resistant, which is independent from body fat and characterized by hyperinsulinemia, it could be hypothesized that there would be an increased bone mass in the patient as a result. Subsequently, increased bone mass could be measured using the wrist circumference method.

AIM

To assess the wrist circumference as an easy-to-detect marker of IR in Congolese women with PCOS.

METHODS

Seventy-two Congolese women with PCOS and seventy-one controls from the same ethnic group, were enrolled in the study (mean age 24.33 ± 5.36 years). Fasting biochemical parameters, and the Homeostasis Model Assessment of insulin resistance (HOMA-IR) and body composition were evaluated. The non-dominant wrist circumference was measured manually, as was the waist circumference (WC), hip circumference, height and weight. Calculated measures included evaluation of body mass index (BMI), Waist-to-Height (WHtR) and Waist-to-hip ratio (WHR). In addition, body composition was assessed by Bioelectrical Impedance Analysis using a body fat analyzer.

RESULTS

The non-dominant wrist circumference was more closely correlated with HOMA-IR (r = 0.346; P = 0.003) and was the best anthropometrical marker correlated with IR (P = 0.011) compared with other anthropometrical markers in women with

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PCOS: Dominant Wrist Circumference (r = 0.315; P = 0.007), Waist Circumference (WC) (r = 0.259; P = 0.028), BMI (r = 0.285; P = 0.016), WHR (r = 0.216; P = 0,068) and WHtR (r = 0.263; P = 0.027). The diagnostic accuracy of the non-dominant wrist circumference for the presence or absence of IR using Receiver-operating characteristic (ROC) curve analysis showed that the area under the ROC curve was 0.72. A cutoff value for the non-dominant wrist circumference of 16.3 cm was found to be the best predictor of IR in Congolese women with PCOS.

CONCLUSION

Non-dominant wrist circumference is, to date, the best anthropometrical marker of IR in Sub-Saharan African women with PCOS. It could be suggested as an easy-to-detect marker for assessing IR.

Key words: Wrist circumference; Insulin resistance; Polycystic ovary syndrome; Congolese women; Sub-Saharan African women; Marker of insulin resistance; Homeostasis Model Assessment of insulin resistance; Easy-to-detect marker

Core tip: In a previous study, we found that insulin resistance (IR), which is independent of the body fat and central distribution in women with polycystic ovary syndrome (PCOS), is commonly found among the African population. Among various markers of IR, the role of anthropometric indicators is obvious in developing countries. Therefore, a more appropriate method that should be easy to perform is sought. In the present study, we found for the first time that non-dominant wrist circumference is not only a marker of IR, but the best anthropometric marker known to date for the assessment of IR in women with PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age[1]. Insulin resistance (IR), the major complication for women with PCOS, is strongly associated with an increased risk of cardiovascular diseases and diabetes and affects 35%-80% of women[2-4]. Early detection of IR could help prevent these complications. However, there is no consensus regarding the most accurate method to predict IR in women with PCOS.

In recent decades, several structural body components have been evaluated in relation to IR[5-9]. Waist circumference (WC), body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) are examples. However, because they are all based on body fat assessment, they cannot accurately predict IR in women with PCOS. Indeed, IR in PCOS in particular is independent of the BMI and body fat distribution[2,3]. Consequently, a more appropriate method that should be easy to perform is sought.

Among various markers of IR, the role of anthropometric indicators is obvious in developing countries[9]. Because of poverty and a lack of suitable laboratories, biological evaluation of IR based on the measurement of insulin or other biological markers is difficult. Therefore, finding a marker that is not based on the measurement of fat, which is anthropometric and easy to perform, has become a challenge. Meeting this challenge has been the basis of our research.

Indeed, in a previous study, we found that IR in women with PCOS, although appearing to be a Western pathology when we look at the currently available literature, is commonly found among the African population[3]. Moreover, one of two Congolese women with PCOS is insulin-resistant[3]. However, many live with this burden and its consequences, and it is not well-treated. Recently, publications have reported on the bone system as a new endocrine organ[10,11]. Indeed, bone has been

found to be involved in glucose metabolism *via* osteocalcin (OC) effects on insulin[11-16]. Osteocalcin, the hormone secreted by osteoblasts, exerts an endocrine regulation of sugar homeostasis by improving insulin sensitivity. It has been shown that in the presence of IR, its compensatory hyperinsulinaemia is associated with increased bone mass, which could be detected by a simple measurement of the wrist circumference (WrC)[17]. Wide WrC has been associated with IR[17-19]. Subsequently, the WrC has been proposed as a new easy-to-detect marker of IR in young obese people[17,20-21].

Given that most women with PCOS are insulin-resistant, independent of fat and characterized by hyperinsulinaemia[2,3,22], we hypothesized that in the presence of IR in Congolese women with PCOS, hyperinsulinaemia might induce increased bone mass that could be detected by the measurement of WrC. Wide WrC should be associated with IR in Congolese women with PCOS. Thus, WrC could be proposed as a new easy-to-detect marker for IR assessment in women with PCOS. The aim of this study was to assess the wrist circumference in Congolese women with PCOS in relation to IR using the Homeostasis Model Assessment as a biological reference marker.

MATERIALS AND METHODS

This prospective case-control study was performed from October 2015 to December 2016 in Kinshasa, the capital city of the Democratic Republic of Congo, and involved 72 women with PCOS and 71 controls. Because the prevalence of PCOS in the Democratic Republic of Congo is unknown, we have taken into account the global prevalence, which varies between 5%-10%, to determine our sample size. Because PCOS is largely unknown in the Democratic Republic of Congo, numerous real cases of PCOS are not found among outpatient clinics. Due to popular beliefs, many PCOS patients are often discouraged from seeing a doctor for numerous reasons: (1) The doctor visit is expensive; (2) Hirsutism is seen as a beautiful trait. In fact, women never consult for hirsutism; (3) Spaniomenorrhoea and/or amenorrhoea are sometimes seen as a normal phenomenon in a woman's life, especially before marriage; and (4) Lack of efficacy of previous treatment received. For these reasons, our PCOS patients were recruited not only from outpatient clinics but also from universities and the community by means of personal interviews and advertising.

The patients were women with PCOS, all African and of reproductive age and from a Congolese ethnic group, without hormonal treatment for the 2 months preceding the study. The study protocol was approved by the ethical committee of the Università Campus Bio-Medico di Roma. Written informed consent was obtained from each subject before entry into the study. PCOS was defined according to the Rotterdam 2003 consensus[1], by the presence of at least two of the following three features: (1) Clinical and/or biochemical signs of hyperandrogenism; (2) Oligomenorrhoea and/or anovulation; and (3) Polycystic ovaries. Clinical hyperandrogenism was defined by a Ferriman-Gallwey score > 8. Age-matched control women came from the same ethnic group. They were of reproductive age, non-hirsute, without a personal or family history of hirsutism and/or endocrine disorders, and not on medical treatment.

Women were excluded if they: (1) Refused to participate in the study; (2) Were pregnant or became pregnant during the study period; (3) Were in the peripubertal period; (4) Were in menopause; or (5) Were using any contraception method, hormonal treatment or insulin sensitizers.

All women underwent a physical examination including an evaluation of the blood pressure, weight, height, wrist circumference, abdominal and hip circumference. All anthropometric measurements were taken by the same examiner to minimize error.

Blood pressure was measured after a 10-minute rest in the sitting position, with the feet on the floor and the arm supported at heart level. Normal values were considered to be < 130/85 mm Hg[1]. The non-dominant wrist circumference was measured with the subjects in a seated position using a tape measure positioned over Lister's tubercle of the distal radius and over the distal ulna[23].

The WC was measured at the end of a normal expiration, at a level parallel to the floor, at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, in the mid axillary line, using stretchresistant tape, with the women relaxed and standing with the feet close together, arms at the side and body weight evenly distributed[24]. The hip circumference was measured at a level parallel to the floor, at the largest circumference of the buttocks[24]. Calculated measures included the BMI, WHtR and WHR.

In addition, body composition was assessed by Bioelectrical Impedance Analysis using a body fat analyser (OMRON BF 511®). This device measures the impedance of each body segment to 50 kHz. It uses electrical impedance with height, weight, age

and gender information to generate body composition data (body fat percentage, visceral fat level and skeletal muscle percentage). The assessment was performed in the morning after a fast of ≥ 3 h, with the patient wearing a light dress and stripped of all metal objects. The women were instructed not to practice vigorous exercise before the test. The BMI was classified according to the WHO criteria as[25]: (1) Normal: 18.5-24.9 kg/m^2; (2) Overweight: 25.0-29.9 kg/m^2; (3) Obese: (a) Class I: 30.0-35.0 kg/m^2; (b) Class II: 35.1-39.9 kg/m^2; (c) Class III: > 40.0 kg/m^2. The WHR was classified as normal if < 0.85 and substantially increased if ≥ 0.85[24]. The WC was classified as normal if < 80 cm and substantially increased if ≥ 80 cm[24].

Biochemistry

The biological measurements included the fasting glucose and insulin. A fasting blood sample was collected from the PCOS and control subjects in the morning and was centrifuged immediately. The serum was stored at -20 °C until analysis. The blood glucose concentration was determined on the day of blood collection by the glucose oxidase method using a glucometer (Freestyle). Insulin was measured using the ELISA method. IR was assessed by Homeostasis Model Assessment of insulin resistance (HOMA-IR) using the following formula:

HOMA-IR = [(glucose in mmol/L) × insulin in μU/mL]/22.5[26,27]

Where glucose is in mmol and has been transformed from mg/dL by the following formula:

Glucose in mmol/L = Glucose (in mg/dL)/18

The normal value of HOMA-IR was ≤ 2.74 mol × μU/L^2, as previously reported[3].

All women with HOMA-IR > 2.74 mol × μU/L^2, were insulin-resistant[3].

Statistical analysis

The statistical analysis was performed using SPSS statistical software (version 16.0). Qualitative data were expressed as the frequency (*n* = number) and proportion (%). Continuous data are expressed as the mean ± standard deviation. The Kolmogorov-Smirnov was used for the normality analysis of the parameters. Student's *t*-test and Chi-square test were used for the comparisons between groups and subgroups of continuous and categorical variables, respectively. Non-parametric tests were used for variables not normally distributed. Logistic regression was performed to analyze the association between the study variables. The odds ratio (OR) was presented with their 95% confidence interval (CI). Statistical significance was expressed as $^aP < 0.05$, $^bP < 0.001$.

RESULTS

Table 1 and Table 2 show the characteristics of our study population. The 72 Women with PCOS and 71 controls participated at all stages of the study. The mean age was similar in both groups and subgroups. There was a significant difference for the Ferriman-Gallwey (F-G) score between women with PCOS and controls as well as for insulinaemia and HOMA-IR (P <0.001). Before performing logistic regression, we studied the correlation between anthropometrical parameters and HOMA-IR. We found that non-dominant wrist circumference was more closely correlated with HOMA-IR (r = 0.346; P = 0.003) than dominant wrist circumference (r = 0.315; P = 0.007), WC (r = 0.259; P = 0.028), BMI (r = 0.285; P = 0.016), WHR (r = 0.216; P = 0.068) or WHtR (r = 0.263; P = 0.027).

In contrast, we found a strong correlation between the dominant WrC, non-dominant WrC, WC, BMI, weight, WHtR and WHR. Because of the severe collinearity and high correlation, we could not use these parameters in the same regression model. Logistic regression analysis was then performed. First, we performed logistic regression using binary HOMA-IR (IR+: HOMA-IR > 2.74; IR-: HOMA-IR ≤ 2.74) as the dependent variable. The non-dominant WrC was significantly associated with IR (P =0.011) (Table 3).

Next, we compared our results using other anthropometrical markers. We replaced the non-dominant WrC with the WC in the model. We observed that the significance disappeared (P = 0.065) (Table 4). We observed the same phenomenon when we replaced the non-dominant wrist circumference with BMI (P = 0.070) (Table 5) and then WHR (P = 0.239) (Table 6) and WHtR (P = 0.068) (Table 7). It appeared that non-dominant wrist circumference was the best anthropometric marker correlated with IR.

We then assessed the diagnostic accuracy of non-dominant wrist circumference for the presence or absence of IR using Receiver-operating characteristic (ROC) curve analysis (Figure 1). As shown, the area under the ROC curve was 0.72. This result indicates that non-dominant wrist circumference has a 72% chance of predicting the presence of IR in women with PCOS. In our search of a cutoff value for non-dominant

Table 1 Clinical and biochemical features of the study subjects

Parameters	PCOS (*n* = 72)	Controls (*n* = 71)	*P* value
Age (yr)	24.4 ± 5.2	24.25 ± 5.5	0.869
Menarche age (yr)	12.97 ± 1.9	12.86 ± 1.8	0.723
Ferriman-Gallwey Score	8.62 ± 6.2	2.32 ± 2.3	< 0.001
Systolic blood pressure (mm Hg)	109.24 ± 17.26	100.86 ±15.27	0.003
Diastolic blood pressure (mm Hg)	71.84 ± 14.11	64.96 ± 12.53	0.003
BMI (kg/m²)	25.23 ± 5.55	23.07 ± 4.52	0.013
WC (cm)	84.28 ± 13.94	78.63 ± 11.60	0.009
WHR	0.81 ± 0.06	0.80 ± 0.05	0.101
WHtR	0.51 ± 0.08	0.48 ± 0.07	0.018
Dominant Wrist Circumference (cm)	15.98 ± 1.15	15.53 ± 0.87	0.009
Non-Dominant Wrist Circumference (cm)	15.80 ± 1.18	15.33 ± 0.87	0.009
Weight (kg)	66.9 ± 16.3	60.8 ± 11.8	0.013
Body fat (%)	35.05 ± 9.6	32.37 ± 8	0.076
Muscle (%)	26.6 ± 4.5	27.9 ± 3	0.042
Visceral fat	4.67 ± 2	3.97 ± 1.7	0.031
Glucose (mg/dL)	86.51 ± 10.3	84.3 ± 8.04	0.155
Insulin (μU/L)	14.91 ± 15.4	6.34 ± 3.8	< 0.001
HOMA-IR (mol × μU/L²)	3.40 ± 4.03	1.33 ± 0.83	< 0.001

PCOS: Polycystic ovary syndrome; IR: Insulin resistance; BMI: Body mass index; WC: Waist circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio; HOMA-IR: Homeostasis Model Assessment of insulin resistance; *n*: Number of participants.

wrist circumference, we found 16.3 cm to be the best predictor of IR in Congolese women with PCOS.

DISCUSSION

To our knowledge, this is the first study that provides evidence that non-dominant wrist circumference can be used as a marker for IR in women with PCOS. Current recommendations for the management of PCOS suggest that given the association with IR, all women with PCOS should be evaluated for the risk of metabolic syndrome and its components, including type 2 diabetes, hypertension, hyperlipidaemia, and the possible risk of clinical events, including acute myocardial infarction and stroke[28]. However, a non-consensus method is provided for the assessment of IR. In contrast, the problem in Sub-Saharan African countries is the diagnosis of IR. The biological evaluation of IR is not only extremely expensive and complicated but also available only in a few laboratories in capital cities. Anthropometrical parameters are, therefore, most recommended[10].

We aimed to assess the non-dominant wrist circumference in relation to IR in Congolese women with PCOS using the Homeostasis Model Assessment for IR as the reference biological index. This choice regarding HOMA-IR was determined by the precedent study performed in Congolese women with PCOS[3] but also because HOMA-IR is an extensively validated marker[4,29-32]. Making a comparison between women with PCOS and the controls, we found a significant difference regarding dominant and non-dominant wrist circumference. This observation corroborates that of Esmaeilzadeh *et al*[33], who found that adolescent girls with PCOS have a higher mean wrist circumference compared to those without PCOS.

We found a positive and significant correlation between non-dominant wrist circumference and IR among women with PCOS. Moreover, non-dominant wrist circumference was the strongest marker associated with HOMA-IR, whereas the WC, BMI, WHR and WHtR were poorly associated with this parameter. This observation was predictable because IR in women with PCOS is independent of body fat[2,3]. Our observation makes non-dominant wrist circumference the best anthropometric marker of IR known to date. The novelty of the WrC as a marker of IR is that it is based on an assessment of IR on bone, not fat[17,20].

This observation also highlights the impact of IR on bone in women with PCOS, opening a new research perspective on this complication in such women. Indeed, to

Table 2 Clinical and biochemical features of the polycystic ovary syndrome subjects with and without insulin resistance

Parameters	PCOS IR+ (*n* = 28)	PCOS IR- (*n* = 44)	*P* value
Age (yr)	25.07 ± 5.67	23.98 ± 4.89	0.388
Menarche age (yr)	12.71 ± 2.03	13.14 ± 1.85	0.367
Ferriman-Gallwey Score	8.04 ± 6.91	9.00 ± 5.87	0.528
Systolic blood pressure (mm Hg)	114.08 ± 22.20	106.59 ± 13.43	0.087
Diastolic blood pressure (mm Hg)	74.62 ± 17.42	70.32 ± 11.89	0.232
BMI (kg/m²)	27.39 ± 6.27	23.90 ± 4.66	0.016
WC (cm)	90.09 ± 15.76	80.58 ± 11.36	0.008
WHR	0.84 ± 0.07	0.80 ± 0.06	0.014
WHtR	0.54± 0.09	0.49 ± 0.07	0.014
Dominant wrist circumference (cm)	16.49 ± 1.27	15.66 ± 0.95	0.005
Non-dominant wrist circumference (cm)	16.33 ± 1.20	15.45 ± 1.03	0.002
Weight (kg)	72.88 ± 18.56	63.26 ± 13.86	0.025
Body fat (%)	38.50 ± 9.44	32.93 ± 9.22	0.017
Muscle (%)	26.30 ± 3.42	26.90 ± 5.09	0.591
Visceral fat	5.48 ± 2.15	4.16 ± 1.75	0.010
Glucose (mg/dL)	93.04 ± 10.34	82.36 ± 7.99	< 0.001
Insulin (μU/L)	26.22 ± 19.99	7.71 ± 2.99	< 0.001
HOMA-IR (mol × μU/L²)	6.26 ± 5.32	1.57 ± 0.63	< 0.001

Data presented as mean ± SD. PCOS: Polycystic ovary syndrome; IR: Insulin resistance; BMI: Body mass index; WC: Waist circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio; HOMA-IR: Homeostasis Model Assessment of insulin resistance; *n*: Number of participants.

date, many publications that have studied the impact of PCOS on bone have mainly focused on the study of bone mineral density[34-38]. Our study focuses on the impact of IR and PCOS status on the hormonal interaction between bone and insulin, suggesting a close relationship among them. Therefore, it is necessary to understand the pathophysiological mechanism of this association to develop appropriate preventive strategies.

Recently, wrist circumference has attracted much attention[17-20,33]. Many authors have found a strong association between the wrist circumference and cardio-vascular risk. Capizzi *et al*[17], studying overweight and obese adolescents, was the first to report that wrist circumference is strongly correlated with fasting insulin levels and insulin-resistance. Mohebi *et al*[39] evaluated the effect of wrist circumference on the risk of incident hypertension and cardiovascular disease (CVD) in an adult population and found that in non-centrally obese women, an increase in wrist circumference was independently associated with both hypertension and cardiovascular disease. Amini *et al*[20], in a study conducted among 1709 participants, found that the association of wrist circumference with cardiometabolic risk factors was significantly positive with waist circumference (P = 0.001), BMI (P = 0.001), and LDL-C (P = 0.01) but significantly inverse with HDL-C (P = 0.001). He suggested that measurement of the wrist circumference can serve as an easy-to-detect clinical marker to identify individuals at risk of cardiometabolic disorders and can be used in large epidemiological studies.

CONCLUSION

In the present study, we found, for the first time, that non-dominant wrist circumference is not only a marker of IR, but the best anthropometric marker known to date, for the assessment of IR in women with PCOS. However, we recognise some limitations of our study, among them, the limited size of our study population. We recommend large-scale studies to validate our observations.

Table 3 Logistic regression examining non-dominant wrist circumference

	B	SE	Wald	df	*P* value	Exp (B)
Age	0.031	0.055	0.311	1	0.577	1.031
Height	-0.052	0.045	1.323	1	0.250	0.950
Diastolic blood pressure (mm Hg)	-0.004	0.021	0.028	1	0.866	0.996
Non-dominant wrist circumference	0.737	0.291	6.424	1	0.011	2.089
Constant	-4.384	6.785	0.417	1	0.518	0.012

B: B coefficient; SE: Standard error; df: Degrees of freedom; Exp (B): Exponentiation of the B coefficient.

Table 4 Logistic regression examining waist circumference

	B	SE	Wald	df	*P* value	Exp (B)
Diastolic blood pressure (mm Hg)	-0.008	0.023	0.118	1	0.731	0.992
Height	-0.020	0.042	0.222	1	0.637	0.980
Age	0.020	0.055	0.133	1	0.715	1.020
WC	0.048	0.026	3.408	1	0.065	1.049
Constant	-1.383	6.739	0.042	1	0.837	0.251

WC: Waist Circumference; B: B coefficient; SE: Standard error; df: Degrees of freedom; Exp (B): Exponentiation of the B coefficient.

Table 5 Logistic regression examining body mass index

	B	SE	Wald	df	*P* value	Exp (B)
Diastolic blood pressure (mm Hg)	-0.004	0.022	0.034	1	0.854	0.996
Height	-0.010	0.041	0.060	1	0.807	0.990
Age	0.036	0.054	0.451	1	0.502	1.037
BMI	0.104	0.057	3.286	1	0.070	1.109
Constant	-2.215	6.653	0.111	1	0.739	0.109

BMI: Body mass index; B: B coefficient; SE: Standard error; df: Degrees of freedom; Exp (B): Exponentiation of the B coefficient.

Table 6 Logistic regression examining waist-to-hip ratio

	B	SE	Wald	df	*P* value	Exp (B)
Diastolic blood pressure (mm Hg)	0.003	0.022	0.025	1	0.873	1.003
Height	-0.002	0.041	0.003	1	0.956	0.998
Age	0.019	0.057	0.110	1	0.740	1.019
WHR	6.009	5.107	1.384	1	0.239	407.060
Constant	-5.891	7.309	0.650	1	0.420	0.003

WHR: Waist-to-hip ratio; B: B coefficient; SE: Standard error; df: Degrees of freedom; Exp (B): Exponentiation of the B coefficient.

Table 7 Logistic regression examining waist-to-height ratio

	B	S.E.	Wald	df	*P* value	Exp (B)
Diastolic blood pressure (mm Hg)	-0.008	0.023	0.121	1	0.728	0.992
Height	0.004	0.041	0.012	1	0.914	1.004
Age	0.020	0.055	0.134	1	0.714	1.021
WHtR	7.878	4.312	3.338	1	0.068	2.638E3
Constant	-5.335	6.920	0.594	1	0.441	0.005

WHtR: Waist-to-height ratio; B: B coefficient; SE: Standard error; df: Degrees of freedom; Exp (B): Exponentiation of the B coefficient.

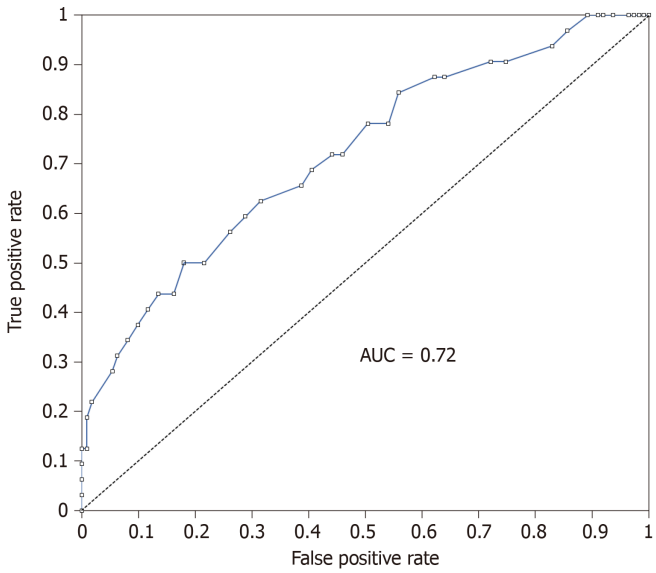

Figure 1 Receiver-operating characteristic curve of the non-dominant wrist circumference cutoff point to predict insulin resistance (defined as Homeostasis Model Assessment of insulin resistance > 2.74 mol × μU/L²) in women with polycystic ovary syndrome. AUC: Area under the curve.

ARTICLE HIGHLIGHTS

Research background

Polycystic ovary syndrome (PCOS) is insulin-resistant and strongly associated with an increased risk of cardiovascular diseases and diabetes in women. Early detection of insulin resistance (IR) could prevent these complications. There is no consensus regarding methods to predict IR in women with PCOS. Some structural body components have been evaluated in relation to IR in PCOS, and IR seems to be independent. In this article we tried for a new easy detectable marker for IR in women affected by PCOS.

Research motivation

We tried to develop a new easy marker for IR in women with PCOS to improve the diagnosis of IR in Sub-Saharan African women.

Research objectives

Our aim was to assess the wrist circumference in women affected by PCOS and living in Kinshasa, the capital city of the Democratic Republic of Congo, in relation to IR using the Homeostasis Model Assessment as a biological reference marker.

Research methods

This study was a prospective case-control study performed from October 2015 to December 2016 in Kinshasa. Seventy-two women with PCOS and 71 controls were enrolled. Parametric and non-parametric statistical test have been used where appropriated. The statistical analysis was performed using SPSS statistical software (version 16.0).

Research results

In this study we have found a significant difference for the Ferriman-Gallwey (F-G) score between the women with PCOS and controls as well as for insulinaemia and HOMA-IR (*P*

<0.001). A strong correlation between the dominant WrC, non-dominant WrC, WC, BMI, Weight, WHtR and WHR have been found. The Receiver-Operating Characteristic (ROC) curve analysis, showed that the non-dominant wrist circumference has a 72% chance of predicting the presence of IR in women with PCOS.

Research conclusions

In the present study for the first time, we showed that the non-dominant wrist circumference is both, a marker of IR, and the best anthropometric marker known, to date for the assessment of IR in women with PCOS.

Research perspectives

This article could open new perspectives between IR and bone homeostasis in women with PCOS.

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REFERENCES

1 **Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group**. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; **19**: 41-47 [PMID: 14688154 DOI: 10.1093/humrep/deh098]

2 **Dunaif A**, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989; **38**: 1165-1174 [PMID: 2670645 DOI: 10.2337/diab.38.9.1165]

3 **Amisi C**, Mputu L, Mboloko E, Bieleli E, Pozzili P. [Biological insulin resistance in Congolese woman with polycystic ovary syndrome (PCOS)]. *Gynecol Obstet Fertil* 2013; **41**: 707-710 [PMID: 24200988 DOI: 10.1016/j.gyobfe.2013.08.002]

4 **DeUgarte CM**, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the Homeostasis Model Assessment. *Fertil Steril* 2005; **83**: 1454-1460 [PMID: 15866584 DOI: 10.1016/j.fertnstert.2004.11.070]

5 **Huxley R**, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. *Eur J Clin Nutr* 2010; **64**: 16-22 [PMID: 19654593 DOI: 10.1038/ejcn.2009.68]

6 **Vazquez G**, Duval S, Jacobs DR, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007; **29**: 115-128 [PMID: 17494056 DOI: 10.1093/epirev/mxm008]

7 **Chouraki V**, Wagner A, Ferrières J, Kee F, Bingham A, Haas B, Ruidavets JB, Evans A, Ducimetière P, Amouyel P, Dallongeville J. Smoking habits, waist circumference and coronary artery disease risk relationship: the PRIME study. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 625-630 [PMID: 18813130 DOI: 10.1097/HJR.0b013e32830fe479]

8 **Mansour AA**, Al-Jazairi MI. Cut-off values for anthropometric variables that confer increased risk of type 2 diabetes mellitus and hypertension in Iraq. *Arch Med Res* 2007; **38**: 253-258 [PMID: 17227737 DOI: 10.1016/j.arcmed.2006.09.014]

9 **Ashwell M**, Gibson S. Waist to height ratio is a simple and effective obesity screening tool for cardiovascular risk factors: Analysis of data from the British National Diet And Nutrition Survey of adults aged 19-64 years. *Obes Facts* 2009; **2**: 97-103 [PMID: 20054212 DOI: 10.1159/000203363]

10 **Karsenty G**, Ferron M. The contribution of bone to whole-organism physiology. *Nature* 2012; **481**: 314-320 [PMID: 22258610 DOI: 10.1038/nature10763]

11 **Schwetz V**, Pieber T, Obermayer-Pietsch B. The endocrine role of the skeleton: background and clinical evidence. *Eur J Endocrinol* 2012; **166**: 959-967 [PMID: 22436399 DOI: 10.1530/EJE-12-0030]

12 **Veldhuis-Vlug AG**, Fliers E, Bisschop PH. Bone as a regulator of glucose metabolism. *Neth J Med* 2013; **71**: 396-400 [PMID: 24127499]

13 **Confavreux CB**, Levine RL, Karsenty G. A paradigm of integrative physiology, the crosstalk between bone and energy metabolisms. *Mol Cell Endocrinol* 2009; **310**: 21-29 [PMID: 19376193 DOI: 10.1016/j.mce.2009.04.004]

14 **Confavreux CB**. Bone: from a reservoir of minerals to a regulator of energy metabolism. *Kidney Int* 2011; **79121**: S14-S19 [PMID: 26746856 DOI: 10.1038/ki.2011.25]

15 **Im JA**, Yu BP, Jeon JY, Kim SH. Relationship between osteocalcin and glucose metabolism in postmenopausal women. *Clin Chim Acta* 2008; **396**: 66-69 [PMID: 18657532 DOI: 10.1016/j.cca.2008.07.001]

16 **Kinjo M**, Setoguchi S, Solomon DH. Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S. sample. *J Clin Endocrinol Metab* 2007; **92**: 4161-4164 [PMID: 17785365 DOI: 10.1210/jc.2007-0757]

17 **Capizzi M**, Leto G, Petrone A, Zampetti S, Papa RE, Osimani M, Spoletini M, Lenzi A, Osborn J, Mastantuono M, Vania A, Buzzetti R. Wrist circumference is a clinical marker of insulin resistance in overweight and obese children and adolescents. *Circulation* 2011; **123**: 1757-1762 [PMID: 21482965 DOI: 10.1161/CIRCULATIONAHA.110.012898]

18 **Derakhshan A**, Tohidi M, Hajebrahimi MA, Saadat N, Azizi F, Hadaegh F. Sex-specific incidence rates and risk factors of insulin resistance and β-cell dysfunction: a decade follow-up in a Middle Eastern population. *Diabet Med* 2017; **34**: 245-252 [PMID: 26996519 DOI: 10.1111/dme.13117]

19 **Stolk RP**, Van Daele PL, Pols HA, Burger H, Hofman A, Birkenhäger JC, Lamberts SW, Grobbee DE. Hyperinsulinemia and bone mineral density in an elderly population: The Rotterdam Study. *Bone* 1996; **18**: 545-549 [PMID: 8805995 DOI: 10.1016/8756-3282(96)00079-8]

20 **Amini A**, Soltanian N, Iraj B, Askari G, Ebneyamin S, Ghias M, Hajian H, Zahed A, Amini M. Association of wrist circumference with cardio metabolic risk factors. *J Pak Med Assoc* 2012; **62**: S34-S36 [PMID: 22768455]

21 **Jahangiri Noudeh Y**, Hadaegh F, Vatankhah N, Momenan AA, Saadat N, Khalili D, Azizi F. Wrist circumference as a novel predictor of diabetes and prediabetes: results of cross-sectional and 8.8-year follow-up studies. *J Clin Endocrinol Metab* 2013; **98**: 777-784 [PMID: 23341488 DOI: 10.1210/jc.2012-2416]

22 **Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group**. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod* 2012; **27**: 14-24 [PMID: 22147920 DOI: 10.1093/humrep/der396]

23 **Nyland J**, Fried A, Maitra R, Johnson DL, Caborn DN. Wrist circumference is related to patellar tendon thickness in healthy men and women. *Clin Imaging* 2006; **30**: 335-338 [PMID: 16919555 DOI: 10.1016/j.clinimag.2006.02.004]

24 **Nishida C**, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist-Hip Ratio. *Eur J Clin Nutr* 2010; **64**: 2-5 [PMID: 19935820 DOI: 10.1038/ejcn.2009.139]

25 **WHO/FAO Diet, nutrition and the prevention of chronic diseases**. *World Health Organ Tech Rep Ser* 2003; **916**: i-viii, 1-149, backcover [PMID: 12768890]

26 **Matthews DR**, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis Model Assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-419 [PMID: 3899825 DOI: 10.1007/BF00280883]

27 **Wallace TM**, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27**: 1487-1495 [PMID: 15161807 DOI: 10.2337/diacare.27.6.1487]

28 **Goodman NF**, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); Androgen Excess and PCOS Society. American Association Of Clinical Endocrinologists, American College Of Endocrinology, And Androgen Excess And Pcos Society Disease State Clinical Review: Guide To The Best Practices In The Evaluation And Treatment Of Polycystic Ovary Syndrome - Part 2. *Endocr Pract* 2015; **21**: 1415-1426 [PMID: 26642102 DOI: 10.4158/EP15748.DSCPT2]

29 **Sawathiparnich P**, Weerakulwattana L, Santiprabhob J, Likitmaskul S. Obese adolescent girls with polycystic ovary syndrome (PCOS) have more severe insulin resistance measured by HOMA-IR score than obese girls without PCOS. *J Med Assoc Thai* 2005; **88** Suppl 8: S33-S37 [PMID: 16856423]

30 **Cebeci F**, Onsun N, Mert M. Insulin resistance in women with hirsutism. *Arch Med Sci* 2012; **8**: 342-346 [PMID: 22662009 DOI: 10.5114/aoms.2012.28563]

31 **Lankarani M**, Valizadeh N, Heshmat R, Peimani M, Sohrabvand F. Evaluation of insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2009; **25**: 504-507 [PMID: 19499403 DOI: 10.1080/09513590902972083]

32 **Wei HJ**, Young R, Kuo IL, Liaw CM, Chiang HS, Yeh CY. Prevalence of insulin resistance and determination of risk factors for glucose intolerance in polycystic ovary syndrome: a cross-sectional study of Chinese infertility patients. *Fertil Steril* 2009; **91**: 1864-1868 [PMID: 18565519 DOI: 10.1016/j.fertnstert.2008.02.168]

33 **Esmaeilzadeh S**, Delavar MA, Amiri M, Khafri S, Pasha NG. Polycystic ovary syndrome in Iranian adolescents. *Int J Adolesc Med Health* 2014; **26**: 559-565 [PMID: 24447981 DOI: 10.1515/ijamh-2013-0335]

34 **Katulski K**, Slawek S, Czyzyk A, Podfigurna-Stopa A, Paczkowska K, Ignaszak N, Podkowa N, Meczekalski B. Bone mineral density in women with polycystic ovary syndrome. *J Endocrinol Invest* 2014; **37**: 1219-1224 [PMID: 25245338 DOI: 10.1007/s40618-014-0175-5]

35 **McBreairty LE**, Zello GA, Gordon JJ, Serrao SB, Pierson RA, Chizen DR, Chilibeck PD. Women With Polycystic Ovary Syndrome Have Comparable Hip Bone Geometry to Age-Matched Control Women. *J Clin Densitom* 2018; **21**: 54-60 [PMID: 28034591 DOI: 10.1016/j.jocd.2016.10.007]

36 **Attlee A**, Nusralla A, Eqbal R, Said H, Hashim M, Obaid RS. Polycystic ovary syndrome in university students: occurrence and associated factors. *Int J Fertil Steril* 2014; **8**: 261-266 [PMID: 25379154]

37 **To WW**, Wong MW. A comparison of bone mineral density in normal weight and obese adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2012; **25**: 248-253 [PMID: 22840935 DOI: 10.1016/j.jpag.2011.12.073]

38 **Mario FM**, do Amarante F, Toscani MK, Spritzer PM. Lean muscle mass in classic or ovulatory PCOS: association with central obesity and insulin resistance. *Exp Clin Endocrinol Diabetes* 2012; **120**: 511-516 [PMID: 22576259 DOI: 10.1055/s-0032-1309006]

39 **Mohebi R**, Mohebi A, Sheikholeslami F, Azizi F, Hadaegh F. Wrist circumference as a novel predictor of hypertension and cardiovascular disease: results of a decade follow up in a West Asian cohort. *J Am Soc Hypertens* 2014; **8**: 800-807 [PMID: 25455005 DOI: 10.1016/j.jash.2014.08.010]

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