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COMMENT

Myosteatosis: a potential missing link between hypertension and metabolic disorder in the Asian population

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Ectopic adipose infiltration in skeletal muscles, or myosteatosis, has been shown to be associated with increase in insulin resistance and increased risk of metabolic disorders and diabetes mellitus (DM) [1]. Myosteatosis is usually evaluated using CT scans to evaluate the attenuation of the skeletal muscles, usually the total abdominal skeletal muscles near the lumbar 3 vetebral area or skeletal muscles of the lower extremities [2, 3]. Studies have shown that increase in the proportion of low attenuation muscles is significantly associated with metabolic disorders, diabetes and hypertension [2, 4].

Several mechanisms can explain the association myosteatosis and insulin resistance. Skeletal muscle is one of major organs that involves in systemic insulin resistance process, as the skeletal muscle is a major site of insulin-stimulated glucose disposal [5]. Diacylglycerol (DAG) and ceramide are two important lipid intermediates considered to involve in development of skeletal muscle insulin resistance [6]. Accumulation of DAG in skeletal muscle activates isoforms of protein kinase C (PKC), leading to decrease in the activities of insulin receptor substrates (IRS)-1 and phosphatidylinositol-3 kinase (PI3K) in the signaling pathway for insulin-stimulated muscle glucose uptake [6]. Ceramide accumulation also antagonize insulin signaling by inhibiting two important actors, Akt (protein kinase B, PKB) and IRS-1, thereby leading to impaired glucose uptake and glycogen synthesis in muscle [6–8]. In addition, excessive ceramide accumulation may induce mitochondrial dysfunction and reactive oxygen species (ROS) generation, which also aggravates insulin resistance in muscle [9, 10].

As myosteatosis is associated with increase in insulin resistance, it is logical to assume that increase in myosteatosis is associated with increased risk in hypertension. Tobago Health Study, a prospective study longitudinal study of 746 normotensive men of African ancestry, supports this hypothesis. During the mean follow up of 6.2 years, decreased skeletal muscle attenuation was associated with newly developed hypertension [2]. However, because there are ethnic differences in the relationship between visceral obesity and cardiometabolic risk profiles, the significant association between myosteatosis and hypertension demonstrated in the Tobago Health Study cannot be generalized to other ethnicities [11]. Against this backdrop, Jung et al. did a cross sectional analysis of 19,766 Korean subjects who underwent abdominal CT scan for health screening in a single center [12]. The results showed that the lowest quartile of normal attenuation muscle area (NAMA)/body mass index (BMI) exhibited 2.3 time and 2.6 times the risk of hypertension in men and women, respectively. This suggests that subjects with higher proportion of intramuscular adiposity were associated with hypertension. There were several limitations of the study that need mention. First, as this was a cross sectional analysis, we do not know whether myosteatosis is the cause of hypertension. Hypertension is associated with sedentary lifestyles, obesity, poor diets and metabolic syndrome, which would most likely increase the degree of myosteatosis. Perhaps an intervention study to demonstrate whether reduction in myosteatosis is associated with reduction in the risk of hypertension is needed as exercise and weight loss have been shown to significantly reduce myosteatosis [13]. Another limitation is

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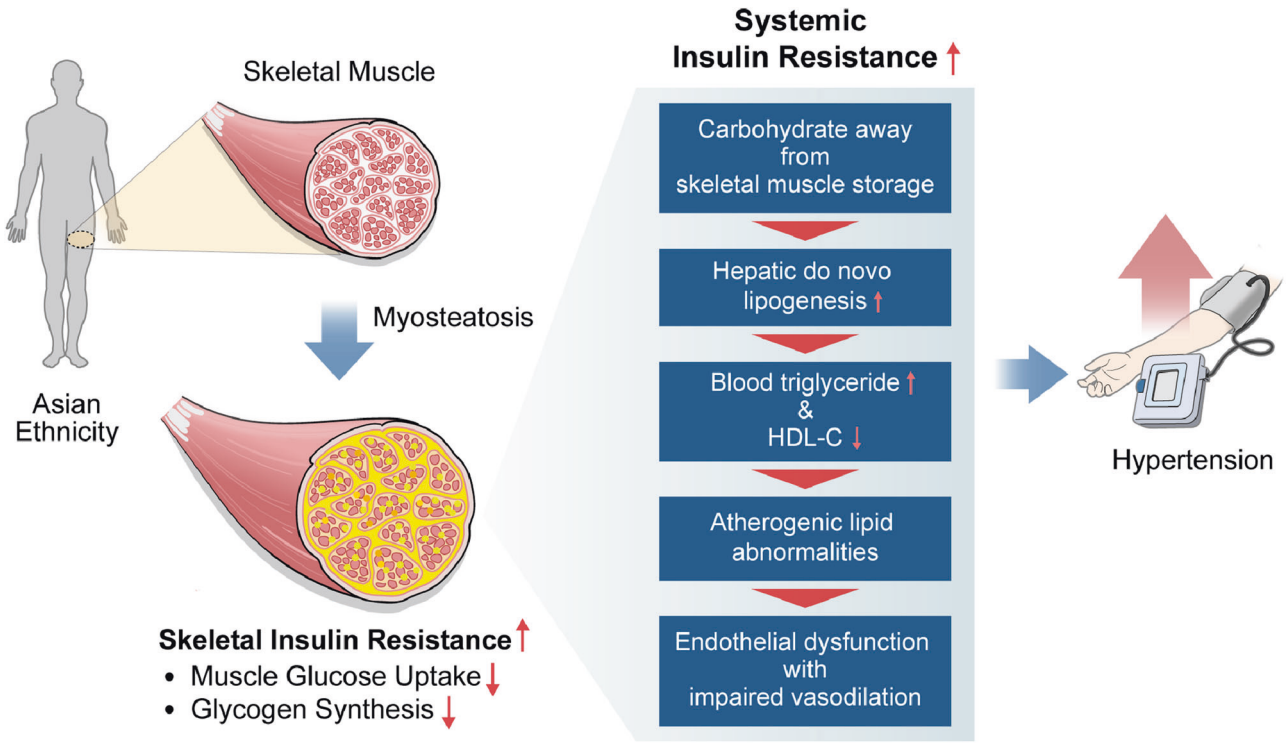
Graphical Opinion

Myosteatosis, by increasing skeletal and systemic insulin resistance, induces endothelial dysfunction and increases the risk of hypertension.



the lack of standard measurements and cutoff values to strictly define myosteatosis. For example, the study by Jung used an artificial algorithm to automatically measure the body composition of the abdominal skeletal muscles, which would not be clinically feasible.

Despite the above mentioned limitations, there are several points of clinical relevance from this study. First, this was the first study to demonstrate a significant association of myosteatosis with hypertension in an Asian population. Second, the study suggests a possible mediation by myosteatosis in the strong association between hypertension and metabolic disorders at a lower BMI in the Asian population [14, 15]. Previous studies have shown that for a given BMI, Asians show a higher body fat percentage compared to Caucasians [16, 17]. Regarding the fat distribution, Asian in general tend to have a higher abdominal and ectopic (such as visceral) fat than Caucasians with similar BMI [18, 19]. Myosteatosis is one of ectopic fat depots as visceral fat and it predicts insulin sensitivity independently of visceral fat [20]. Skeletal muscle insulin resistance induced by myosteatosis plays a role in the development of systemic insulin resistance and metabolic syndrome [21]. Skeletal muscle insulin resistance is characterized by reduced muscle glucose uptake and glycogen synthesis which changes the pattern of ingested carbohydrate away from storage in skeletal muscle into hepatic de novo lipogenesis [21]. Subsequently, increased hepatic de novo lipogenesis results in increase in triglyceride concentration and decrease in high-density lipoprotein concentration, promoting atherogenic dyslipidemia [21]. Atherogenic lipid abnormalities cause endothelial dysfunction that impairs vasodilation to appropriate stimuli and eventually increases blood pressure [22]. Indeed, in a cross sectional analysis of 20,659 participants who underwent abdominal CT, metabolically healthy subjects had significantly higher NAMA and NAMA/total abdominal muscle area (TAMA) compared to metabolically unhealthy subjects, with the NAMA/TAMA index being independently associated with metabolically unhealthy phenotypes in non-obese individuals [23]. This suggests that not only the quantity but also the quality of the muscles are important for maintenance of metabolically healthy status.

Perhaps, the high prevalence of hypertension in the Asian population despite the relatively lower BMI and lower prevalence of obesity may partly be due to the relatively higher visceral fat and myosteatosis. However, studies about ethnic difference in the degree of myosteatosis between Asian and Caucasian are limited and have shown conflicting results depending on the region of Asian population [1, 18]. In addition, the relation between

intramyocellular lipid content and insulin sensitivity differed between ethnicity [24]. Thus, future studies are required to compare the ethnic difference in myosteatosis and its impact on insulin resistance for a given BMI.

Compliance with ethical standards

Conflict of interest ML has received lecture honoraria from JW Pharmaceutical Corporation, Boryung Corporation, Eli Lilly and Company, Merck Sharp & Dohme, HK inno.N, Servier Korea, Handok Inc., and Daewoong Pharmaceutical. SP has received honorarium from Pfizer, Viatris, Boryoung, Hanmi, Daewoong, Donga, Celltrion, Servier, Daiichi Sankyo, Chong Kun Dang and Daewon. SP also has received research grant from Daiichi Sankyo.

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