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ORIGINAL ARTICLE

Improvement in endothelial function by lifestyle modification focused on exercise training is associated with insulin resistance in obese patients

Satoshi Kurose[a,b,*], Hiromi Tsutsumi[a], Yutaka Yamanaka[a], Hiromi Shinno[a], Takumi Miyauchi[c], Atsuko Tamanoi[c], Masaru Imai[d], Izuru Masuda[d], Yutaka Kimura[a,c]

[a] *Department of Health Science, Graduate School of Medicine, Kansai Medical University, 2-3-1, Shinmachi, Hirakata, Osaka, 573-1191, Japan*
[b] *Disease Prevention Center, Ijinkai Takeda General Hospital, 28-1, Ishidamoriminamimachi, Fushimi-ku, Kyoto, 601-1495, Japan*
[c] *Health Science Center, Kanasai Medical University, 2-3-1, Shinmachi, Hirakata, Osaka, 573-1191, Japan*
[d] *EBM Center for Preventive Medicine, Takeda Hospital Group, 277, Aburanokojicho, Aburanokojidori Shimouotana — Sagaru, Shimogyo-ku, Kyoto, 600-8231, Japan*

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Summary A new method to evaluate endothelial function, namely, reactive hyperemia peripheral arterial tonometry (RH-PAT), has been developed. RH-PAT is an index of endothelial function, indicating initial atherosclerotic lesions. The present study aimed to investigate the effect of lifestyle modification with a focus on exercise training on RH-PAT in obese patients. We studied 43 obese patients (body mass index $\geqq$ 30). RH-PAT was measured, and the RH-PAT index was calculated as a ratio of the digital pulse volume during reactive hyperemia divided by that at baseline. Further, we assessed body composition, arterial stiffness, insulin resistance, adipocytokine levels, and exercise tolerance. The exercise program consisted of 30 min on a cycle ergometer or treadmill, 3 times per week for 6 months. Training intensity was adjusted to the anaerobic threshold. Significant improvements were observed in the RH-PAT index following exercise training. We noted a significant reduction in weight, body fat percentage, and leptin values, and a significant increase in adiponectin levels and exercise tolerance. An abnormal baseline RH-PAT index was observed in 24 patients (55.8%); however, the improvement rate was

* Corresponding author at: Department of Health Science, Graduate School of Medicine, Kansai Medical University, 2-3-1, Shinmachi, Hirakata, Osaka, 573-1191, Japan. Tel.: +81 72 804 2821; fax: +81 72 804 2821.
E-mail address: sato_itsu@yahoo.co.jp (S. Kurose).

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higher in these patients than in patients with normal RH-PAT index values. Stepwise multiple regression analysis revealed that changes in insulin resistance (△HOMA-IR) were independently correlated with changes in the RH-PAT index. Our results indicate that lifestyle modification with a focus on exercise training improved the RH-PAT index in obese patients. Patients with abnormal RH-PAT index values before lifestyle modification with exercise training demonstrated a high rate of improvement following exercise. Further, our results suggest that insulin resistance was the only independent factor influencing improvement in endothelial function.

Introduction

Worldwide, the incidence of obesity is increasing because of lack of exercise and changes in lifestyle. Obesity is associated with hypertension, dyslipidemia, and diabetes, and raises the risk of coronary heart disease and stroke [1—3]. Moreover, obesity facilitates the occurrence of diabetes mellitus, which can induce cardiovascular disease via endothelial dysfunction. In obese patients with a body mass index (BMI) $\geqq$ 30, the risk of coronary heart disease is two-fold higher than in individuals with BMI between 23.0 and 24.9 [1].

Atherosclerosis begins with an initial lesion that progresses to arterial stiffness, atherogenesis, and plaque rupture. Atherosclerosis in obese patients may be caused by endothelial dysfunction resulting from insulin resistance. In addition, obese individuals show lower arterial compliance than normal individuals, with reportedly higher arterial stiffness [4]. The most important aim of weight loss in an obese patient is controlling the progression of atherosclerosis, which subsequently reduces the risk of cardiovascular events by ameliorating endothelial dysfunction.

The gold standard for evaluating endothelial function is vasodilatation following acetylcholine injection in the coronary artery or the brachial artery. Vasodilatation of vascular smooth muscle cells occurs through the medium of nitric oxide (NO) produced by arginine during signal transmission from acetylcholine receptors. However, this is an invasive method. Further, NO, prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factor (EDHF) are known to be endothelium-dependent relaxing factors released by endothelial cells in response to shear stress [5,6]. Vasodilatation that occurs in response to shear stress is known as flow-mediated dilatation (FMD); this has attracted attention as a noninvasive method for evaluating endothelial function [7,8].

FMD is measured by assessing brachial artery diameter using an ultrasonic probe after cuff occlusion in the upper arm [9,10]. However, this method presents several challenges, including technical issues during measurement; further, it cannot exclude the influence of the sympathetic nervous system. Recently, Kuvin et al. [11] described a new method for evaluating endothelial dysfunction, known as reactive hyperemia peripheral arterial tonometry (RH-PAT). This noninvasive, automatic method effectively excludes sympathetic activity and is a quantitative clinical test that can digitally measure the hyperemic response. RH-PAT has been correlated with FMD [12]; however, it has been reported that the increase in coronary blood flow following acetylcholine infusion in the coronary artery is more strongly correlated with RH-PAT than with FMD [13,14]. In addition, RH-PAT does not require extensive training and is reproducible, even when measured by a beginner.

Exercise has been reported to be one of the primary means of improving endothelial function [15]. The rate of improvement in endothelial function following aerobic exercise is reported to be associated with changes in exercise tolerance [16,17]. However, it has also been reported that high-intensity interval training is more useful than aerobic exercise for improving endothelial function [18]. The effects of regular exercise in obese patients are well known [19—22]; further, endothelial function in severely obese patients is known to improve following exercise [23]. Obese patients (BMI $\geqq$ 30) are somewhat uncommon in Japanese society; therefore, few reports have described the effects of exercise on arteriosclerosis in this population. Furthermore, no study has examined the changes in endothelial function by using the RH-PAT index following lifestyle changes without medical therapy for the treatment of obesity. Therefore, the present study aimed to investigate the effects