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Akihiko Kawaura[*] Noritoshi Tanida[†] Masato Kamitani[‡]

Junichi Akiyama[**] Masatoshi Mizutani[††] Naoko Tsugawa[‡‡]

Toshio Okano[§] Eiji Takeda[¶]

[*]Department of Physical Therapy, School of Health Science, KIBI International University,

[†]Department of Medical Humanities, Yamaguchi University Graduate School of Medicine,

[‡]Takahashi Central Hospital,

[**]Department of Physical Therapy, School of Health Science, KIBI International University,

[††]Department of Physical Therapy, School of Health Science, KIBI International University,

[‡‡]Department of Hygienic Sciences, Kobe Pharmaceutical University,

[§]Department of Hygienic Sciences, Kobe Pharmaceutical University,

[¶]Department of Clinical Nutrition, Institute of Health Biosciences, The University of Tokushima Graduate School,

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Abstract

We examined the effect of leg hyperthermia on oxidative stress in bedridden subjects with type 2 diabetes mellitus using 15-min sessions of far infrared rays over a two-week period. Four subjects (male 1, female 3) incapacitated by a stroke were recruited for this study. All patients were admitted to Takahashi Central Hospital and ate the same hospital meals. Fasting plasma glucose, HbA1c, tumor necrosis factor (TNF)alpha, free fatty acid, leptin, adiponectin and plasma 8-epi-prostaglandin F2alpha (8-epi-PGF2alpha) levels as a marker of oxidative stress were measured on admission, just before and 2 weeks after local heating of the leg. Results showed that plasma total 8-epi-PGF2alpha levels were decreased significantly while TNFalpha levels were increased significantly. On the other hand, glucose, HbA1c, free fatty acid, leptin and adiponectin levels were not changed during the study period. These results suggest that repeated leg hyperthermia may protect against oxidative stress.

KEYWORDS: type 2 diabetes mellitus, leg hyperthermia, oxidative stress, 8-epi-prostaglandin F2?

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Case Report

The Effect of Leg Hyperthermia Using Far Infrared Rays in Bedridden Subjects with Type 2 Diabetes Mellitus

Akihiko Kawaura[a,e]*, Noritoshi Tanida[b], Masato Kamitani[c], Junichi Akiyama[a], Masatoshi Mizutani[a], Naoko Tsugawa[d], Toshio Okano[d], and Eiji Takeda[e]

[a]Department of Physical Therapy, School of Health Science, KIBI International University, Takahashi, Okayama 716-8508, Japan, [b]Department of Medical Humanities, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi 755-8505, Japan, [c]Takahashi Central Hospital, Takahashi, Okayama 716-0033, Japan, [d]Department of Hygienic Sciences, Kobe Pharmaceutical University, Kobe 658-8558, Japan, and [e]Department of Clinical Nutrition, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima 770-8503, Japan

We examined the effect of leg hyperthermia on oxidative stress in bedridden subjects with type 2 diabetes mellitus using 15-min sessions of far infrared rays over a two-week period. Four subjects (male 1, female 3) incapacitated by a stroke were recruited for this study. All patients were admitted to Takahashi Central Hospital and ate the same hospital meals. Fasting plasma glucose, HbA1c, tumor necrosis factor (TNF)α, free fatty acid, leptin, adiponectin and plasma 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) levels as a marker of oxidative stress were measured on admission, just before and 2 weeks after local heating of the leg. Results showed that plasma total 8-epi-$PGF_{2\alpha}$ levels were decreased significantly while TNFα levels were increased significantly. On the other hand, glucose, HbA1c, free fatty acid, leptin and adiponectin levels were not changed during the study period. These results suggest that repeated leg hyperthermia may protect against oxidative stress.

Key words: type 2 diabetes mellitus, leg hyperthermia, oxidative stress, 8-epi-prostaglandin $F_{2\alpha}$

Epidemiological studies on diabetes mellitus have indicated that the number of patients with diabetes mellitus is gradually increasing in Japan along with the development of a more sedentary society and westernization of food intake (high-fat diet; HFD) [1]. Since the prevalence of diabetes mellitus increases with aging, the proportion of individuals with diabetes mellitus aged over 60 exceeds two-thirds of the estimated total number of patients (7.40 million in 2002) in Japan, where the society is aging rapidly [1]. Diabetes is a risk factor of cerebral infarcts, especially in the elderly [2]. Therefore, there are many patients with diabetes mellitus and cerebral infarction in Japan. Regular exercise is regarded as one of the cornerstones in the management of patients with type 2 diabetes mellitus. In part, the recommendation for exercise is aimed at improving insulin sensitivity [3]. However, many older patient are not able to exercise sufficiently. Systemic thermal therapy has attracted special interest as a potential alternative: it has been examined in an animal diabetic model [4], but has not been studied extensively in patients with diabetes mellitus.

In humans, oxidative stress increases with diabetes [5], and repeated dry sauna therapy with far infrared rays decreased urinary levels of 8-epiprosta-

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*Corresponding author. Phone:+81-86-622-9204; Fax:+81-86-622-9204
E-mail:kawaura@kiui.ac.jp (A. Kawaura)

glandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), a marker of oxidative stress [6]. Oxidative stress has been defined as the deleterious processes resulting from an imbalance between the formation of reactive oxygen species (ROS) and the organism's endogenous antioxidant defenses [7]. Antioxidant compounds have a marked insulin-sensitizing effect [8]. Therefore, sauna therapy in humans may be able to improve insulin sensitivity in diabetic patients. However, it is difficult for old patients incapacitated by stroke to undergo regular exercise and sauna therapy. It was reported that the degree of increase in rectal temperature when legs were immersed in bath water of 42 degrees C for 30 min might be the same as that found for whole-body hyperthermia [9]. We hypothesized that repeated leg hyperthermia would decrease oxidative stress, and lead to improved insulin resistance. Therefore, we examined the effect of leg hyperthermia using far infrared rays on oxidative stress in bedridden subjects with diabetes mellitus.

Case Report

Cases. Four subjects (male 1, female 3) with type 2 diabetes mellitus incapacitated by stroke were recruited for this study (Table 1). Neither ARB (angiotensin-II receptor blocker) nor statin was being given. All were non-smokers. The study was performed after obtaining written informed consent from all subjects, and was approved by the Ethics Committee of Takahashi Central Hospital. All patients were admitted to Takahashi Central Hospital and ate the same hospital meals during a 4-week period. Two weeks after the admission to the hospital, all patients started to receive local heating of the leg. The lower extremities of the patients were placed in a supine position in the heater (Daiugin Rainbow RE-580; wavelength: 8 microns; Dairin Co. Ltd., Osaka, Japan) to keep the legs warm and treated with local heating of the leg using far infrared rays for 15 minutes every day for 2 weeks. The temperature of the skin surface reached 43℃ at 7 min after heating and was kept at 43℃ for 8 min. Body weight, body mass index (BMI), heart rate, blood pressure, hematocrit, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, fasting plasma glucose, HbA1c, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor alpha (TNFα), free fatty acid, leptin, adiponectin and plasma 8-epi-$PGF_{2\alpha}$ levels as markers of oxidative stress [10] were measured on admission, just before and just after the 2-week treatment of daily leg hyperthermia. Levels of serum TNFα, leptin, adiponectin, plasma 8-epi-$PGF_{2\alpha}$ and other routine laboratory data were obtained by measurement through commercial diagnostic facilities (BML Co. Ltd., Tokyo, Japan). Serum TNFα, adiponectin and plasma 8-epi-$PGF_{2\alpha}$ levels were determined by enzyme immunoassay using Quantikine HS human TNF-α ELISA Kit (Funakoshi Co. Ltd., Tokyo, Japan), Human Adiponectin ELISA Kit (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) and Isoprostane Oxidative Stress Assay Kit B (Funakoshi Co. Ltd., Tokyo, Japan), respectively, and the serum leptin level was measured by radioimmunoassay (HUMAN LEPTIN RIA KIT, Cosmic Corporation Co. Ltd., Tokyo, Japan). Statistical comparisons were made with the 2-tailed paired Student *t*-test. *P* values of less than 0.05 were considered statistically significant.

Summary of 4 cases. Laboratory findings of the patients at admission were almost identical with

Table 1 Characteristics of the subjects

	Case 1	Case 2	Case 3	Case 4
Sex	female	male	female	female
Age	74	87	71	77
Chief focus	cerebral infarction	cerebral infarction	cerebral hemorrhage	cerebral infarction
Symptom	right hemiplegia	right hemiplegia	left hemiplegia	left hemiplegia
Dementia	slight	moderate	moderate	slight

Dementia was assessed based on Clinical Dementia Rating (CDR).

those at the start of the study 2 weeks later. There was no significant difference in body weight, BMI, heart rate, blood pressure, hematocrit, total cholesterol, HDL cholesterol, triglyceride, BUN, creatinine, AST and ALT before and after the two-week treatment using local heating of the leg (Table 2). Plasma 8-epi-$PGF_{2\alpha}$ levels were significantly decreased ($p < 0.05$, Fig. 1). Fasting plasma glucose, HbA1c, free fatty acid, leptin and adiponectin were not changed except for the significant increase of TNFα (Table 3). No patient reported feeling ill during leg hyperthermia.

Discussion

In an animal model of diabetes, whole-body hyperthermia-treated db/db mice showed a significant decrease in fasting blood glucose level and the

Table 2 Clinical and laboratory findings in 4 cases before and after 2 weeks of local heating of the leg

	Case 1 (74 years, F)		Case 2 (87 years, M)		Case 3 (71 years, F)		Case 4 (77 years, F)	
	Before	After	Before	After	Before	After	Before	After
Body weight (kg)	50.1	50.4	51.5	52.5	32.7	32.2	39.5	39.2
Body mass index (kg/m^2)	25.2	25.4	19.9	20.3	16.0	15.7	17.8	17.7
Heart rate (beats/min)	82	90	66	60	90	86	64	64
Systolic blood pressure (mmHg)	134	133	148	126	130	149	118	115
Diastolic blood pressure (mmHg)	60	82	67	71	64	72	53	81
Hematocrit (%)	36.1	36.2	47.1	39.0	36.1	35.3	49.8	41.5
Total cholesterol (mg/dl)	166	162	159	129	215	188	237	137
HDL cholesterol (mg/dl)	38	35	72	47	77	65	68	22
Triglycerides (mg/dl)	191	168	51	52	98	81	99	95
BUN (mg/dl)	23.0	21.4	11.7	15.2	15.2	12.1	32.1	60.0
Creatinine (mg/dl)	0.59	0.65	0.43	0.45	0.30	0.28	2.05	2.65
AST (IU/l)	21	20	28	25	31	26	24	19
ALT (IU/l)	21	16	26	25	31	20	14	12

Table 3 Fasting plasma glucose, HbA1c, TNFα, free fatty acid, leptin, and adiponectin of 4 cases before and after 2 weeks of local heating of the leg

	Values*	
	Before	After
Fasting plasma glucose (mg/dl)	99.3 ± 16.5	147.0 ± 61.0
HbA1c (%)	6.15 ± 1.10	6.23 ± 1.02
TNFα (pg/ml)	1.32 ± 0.86	2.42 ± 1.27**
Free fatty acid (mEq/l)	0.60 ± 0.27	0.50 ± 0.10
Leptin (ng/ml)	7.73 ± 8.29	9.88 ± 10.3
Adiponectin (μg/ml)	25.9 ± 25.5	24.6 ± 24.8

*Values are means ± SD.

**TNFα significantly increased after 2 weeks of local heating of the leg ($p < 0.05$).

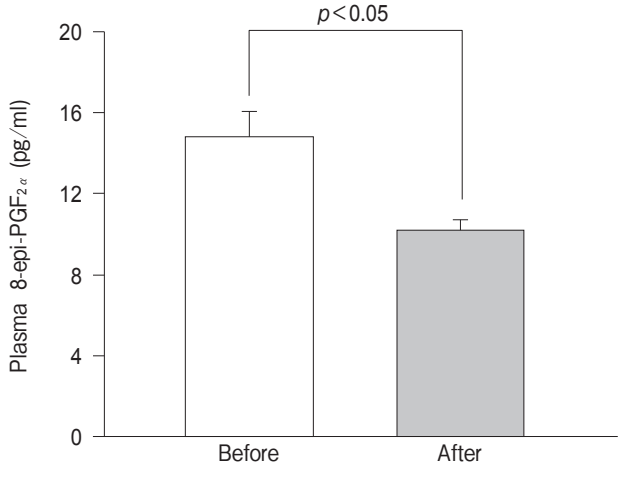

Fig. 1 Plasma 8-epi-$PGF_{2\alpha}$ levels before and after a 2-week treatment of daily 15-min local heating of the leg. The plasma 8-epi-$PGF_{2\alpha}$ level significantly decreased after the 2-weeks leg hyperthermia treatment (2-tailed paired Student *t*-test).

improvement in insulin sensitivity as compared with untreated db/db mice [4]. However, sauna therapy in humans did not improve fasting glucose levels because a large majority of subjects in the study were not diabetic [6]. Results from treatment by sauna therapy and local heating of the leg in patients with diabetes mellitus have not been reported in the literature. In this study, plasma 8-epi-$PGF_{2\alpha}$ levels as a marker of oxidative stress [10] were significantly decreased after local heating of the leg. This is the first report to show that local heating of the leg in diabetes mellitus appeared to cause a significant decrease in oxidative stress. Rectal temperature has been shown to rise when legs are immersed in bath water of 42℃ for 30 min [9]. Therefore, the mechanism of local heating of the leg is thought to be similar to that of sauna therapy [6], although the exact mechanism for this observation is not elucidated. Our results were in accord with the Masuda's hypothesis [6] that the reduction in oxidative stress by repeated sauna therapy may be related to the increase of superoxide dismutase (SOD) and glutathione peroxidase (GPX), which are antioxidants involved in shear stress responses.

In humans, oxidative stress is reported to increase in patients with diabetes [5]. The pathogenesis of oxidative stress in skeletal muscle insulin resistance involves multiple processes; mounting evidence has suggested that an increased release of TNFα and a decrease in adiponectin [8, 11] or a reduction of endothelial nitric oxide synthase (eNOS) bioactivity [12] in the skeletal muscle are involved in this process. An increased release of TNFα would inhibit insulin signaling. Specifically, TNFα confers insulin resistance by promoting phosphorylation of serine residues on insulin receptor substrate 1 (IRS-1), thereby diminishing subsequent insulin-induced tyrosine phosphorylation of IRS-1. Additionally, a decrease in adiponectin would result in the reduction of AMP-activated protein kinase (AMPK) activation and glucose uptake [8]. Regarding the reduction in oxidative stress by antioxidant compounds [8], although antioxidant supplementation in severely insulin-resistant rodents has been reported to increase adiponectin and decrease circulating TNFα levels [8], the same relationship does not appear to hold in humans. For example, vitamin E supplementation in obese individuals failed to increase plasma adiponectin levels [13] or to vary plasma concentrations of TNFα [14]. In this study, repeated leg hyperthermia decreased plasma total 8-epi-$PGF_{2\alpha}$ levels as a marker of oxidative stress [10], but the changes in adiponectin were analogous to those in previous reports on humans [13]. Unexpectedly, TNFα levels were increased significantly. Heatstroke induced by exposing rats to a high blanket temperature (43℃) increased serum and tissue TNFα levels [15]. Thus, two-week leg hyperthermia probably induced an increase of TNFα that overpowered the decrease of TNFα due to decreased oxidative stress, resulting in our finding of elevated TNFα levels, although the exact mechanism was not clear. Probably, a longer time course may be necessary to elucidate the effect of these compounds in leg hyperthermia.

Repeated sauna therapy upregulated mRNA and protein expression of arterial eNOS in hamsters [16, 17]. Duplain indicated that eNOS played a major role in the regulation of insulin sensitivity [18]. Repeated sauna therapy may protect against oxidative stress [6]; local heating of the leg may likewise be able to prevent and to improve skeletal muscle insulin resistance through eNOS expression following the decreased oxidative stress.

Recently, elevating heat shock protein (HSP) 72 by heat treatment was shown to protect mice against diet- or obesity-induced hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance [19]. It was also determined that the Jun NH_2-terminal kinase (JNK) induced insulin resistance through mediating serine phosphorylation on IRS-1 [20] while HPS72 suppressed activation of JNK [21]. A further investigation with more subjects is necessary to clarify the precise mechanisms of our findings in view of the many physiological actions of local heating; however, our results may lead to the development of a new approach to improving skeletal muscle insulin resistance in bedridden subjects with type 2 diabetes mellitus.

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