RESEARCH ARTICLE

High-fat diet reduces levels of type I tropocollagen and hyaluronan in rat skin

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Received: January 13, 2010
Revised: March 11, 2010
Accepted: March 17, 2010

Although it is known that nutritional conditions affect the skin function, little information is available on the effect of a high-fat (HF) diet on skin. In this study, Sprague–Dawley rats were fed HF diets for 28 days, and we investigated the effect of this diet on type I tropocollagen and hyaluronan in rat skin. The HF diets reduced the levels of type I tropocollagen, *COL1A1* mRNA, hyaluronan, and *rat hyaluronan synthase* (*rhas*)*2* mRNA, which play a primary role in hyaluronan synthase in the dermis. However, *rhas3* mRNA level in the skin was increased. The HF diets also decreased the skin mRNA expression of *transforming growth factor* (*TGF*)-*β1*, which enhances the expression of *COL1A1* and *rhas2* mRNA and decreases *rhas3* mRNA expression, and decreased the hepatic mRNA expression of *insulin-like growth factor (IGF)-I*, which enhances *COL1A1, rhas2,* and *TGF-β1* mRNA expression. The serum level of adiponectin, which promotes the syntheses of type I collagen and hyaluronan, was decreased in the HF diet groups. These findings suggest that an HF diet reduces the levels of type I tropocollagen and hyaluronan in the skin by suppressing the action of TGF-β1, IGF-I and adiponectin, and these effects are deleterious for skin function.

Keywords:
Adiponectin / Collagen / High-fat diet / Hyaluronan / Transforming growth factor-β1

1 Introduction

Obesity is a state in which abnormal amounts of fat accumulate in the adipose tissues. The prevalence of obesity is increasing in most countries around the world. In Japan, the prevalence of preobesity (BMI of 25–29.9 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) is 24.5% and 2.3% in men aged $\geq$20 years and 17.8 and 3.4% in women aged $\geq$20 years, respectively [1]. A major cause of obesity is the consumption of a high-calorie diet combined with the decrease in energy expenditure associated with a modern lifestyle [2, 3]. In particular, fat-rich diets are generally associated with the development of obesity and abdominal visceral fat accumulation [4]. Diet-induced obesity causes not only lifestyle-related diseases such as diabetes mellitus and hyperlipidemia but is also associated with skin disorders, including delayed wound healing and a variety of dermatoses [5–7]. Furthermore, Ezure and Amano [8] recently reported that increased fat accumulation in subcutaneous adipose tissue impaired dermal function in mice with obesity induced by a high-fat (HF) diet. However, the molecular mechanism underlying the alteration of skin biomechanical characteristics such as dermal layer thickness and elasticity by HF diets is not well understood.

The skin is composed of two layers – the dermis and epidermis – which consist of stratified squamous epithelial and connective tissues, respectively. The skin also contains large amounts of extracellular matrix components such as collagen and hyaluronan, which are produced mainly by fibroblasts and/or keratinocytes and protect the body from various external insults. Collagen fibers make up approximately 75% of the dry weight of the dermis, and type I collagen accounts for 80% of the total collagen in the adult human dermis [9]. The major structural component of type I

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Abbreviations: AdipoR, adiponectin receptor; **HAS,** hyaluronan synthase; **HF,** high-fat; **IGF-I,** insulin-like growth factor-I; **IGFBP-3,** insulin-like growth factor binding protein; **rhas,** rat HAS; **TGF-β1,** transforming growth factor-β1

collagen is composed of two α1 (I) chains and one α2 (I) chain; these chains are the products of two genes (*COL1A1* and *COL1A2*). Type I collagen imparts tensile strength and stability to the dermis [10]. In contrast, hyaluronan is a large nonsulfated glycosaminoglycan made up of alternate repeats of two sugar units, *N*-acetyl glucosamine, and glucuronate. Hyaluronan retains moisture in the skin, facilitates the transport of ion solutes and nutrients, and promotes wound healing. The skin contains the largest concentration of hyaluronan in the body (approximately 56%) [11]. In mammals, hyaluronan is synthesized by isoforms of hyaluronan synthase (HAS), namely, HAS1, HAS2, and HAS3; these synthases have specific properties and are the products of distinct genes that differ in tissue distribution and regulation [12]. For example, HAS2 is the major producer of hyaluronan in the dermis, whereas HAS3 is the major hyaluronan producer in the epidermis. Thus, collagen and hyaluronan play important roles in the formation of scaffolds promoting tissue repair or regeneration and biological functions such as cellular proliferation and migration in the skin. Therefore, we have focused on type I collagen, hyaluronan, and the molecules involved in the skin after the consumption of HF diets.

In the present study, we examined the levels of type I tropocollagen, which polymerizes to microfibrillar collagen to initiate aggregation, and hyaluronan in the skin of rats fed HF diets containing various fat levels. We also measured the mRNA levels of the genes involved in synthesizing type I collagen and hyaluronan in the skin of these rats. The HF diets were designed to enable comparisons with the amount of dietary fat most commonly consumed by humans [13]. To investigate the mechanism by which an HF diet regulates the production of type I tropocollagen and hyaluronan, we measured the gene expression levels of transforming growth factor (*TGF*)-*β1*, *insulin-like growth factor* (*IGF*)-*I*, and *insulin-like growth factor binding protein* (*IGFBP*)-*3* by using quantitative PCR and also determined the serum adiponectin concentration by using ELISA.

2 Materials and methods

2.1 Materials

Hybond-ECL and ECL Western Blotting Detection Reagents were obtained from GE Healthcare UK (Little Chalfont, England). An anti-rat type I collagen polyclonal antibody was obtained from Rockland Immunochemicals (Gilbertsville, PA, USA). Hyaluronan and hyaluronidase from *Streptomyces hyalurolyticus* were purchased from Seikagaku (Tokyo, Japan), and actinase E from *Streptomyces griseus* was obtained from Kaken Pharmaceutical (Tokyo, Japan). Microcon YM-30 and Centriplus YM-30 were obtained from Millipore (Bedford, MA, USA). A High-Capacity cDNA Reverse Transcription Kit, a TaqMan universal PCR master mix core reagent kit, and TaqMan Gene Expression Assays kits were obtained from Applied Biosystems (Foster City, IN, USA). A mouse/rat adiponectin ELISA kit was purchased from Otsuka Pharmaceutical (Tokyo, Japan).

2.2 Animals and diets

Four-week-old male Sprague–Dawley rats (CLEA, Tokyo, Japan) were individually housed in stainless steel cages and kept in an animal room at 23–25°C and 50–56% humidity under a 12-h light cycle (lights on 8:00–20:00). The animals had free access to food and drinking water. After acclimatization to a normal diet based on AIN-76 feed composition [14] for 1 wk, the animals were divided into 6 groups of 5 individuals (control group (CO; corn oil 5%) and lard 5, 10, 15, 20, and 25% groups) and fed for 28 days. Lard-containing diets were prepared by replacing corn oil and sucrose with lard (Table 1). The percentages of fat energy/total energy in the CO and lard 5, 10, 15, 20, and 25% diets were 12, 12, 22, 31, 39, and 46%, respectively. The animals were dissected on the final day of the experimental period under anesthesia with sodium pentobarbital (5.8 mg/100 g body weight). Serum, to determine adiponectin concentration, was prepared by centrifuging blood samples (3 000 rpm, 4°C, 20 min). The liver was washed with physiological saline, rapidly frozen in liquid nitrogen, and then used for mRNA determination. The skin was rapidly frozen in liquid nitrogen and then used for measuring the level of α1(I) tropocollagen, hyaluronan, and various mRNAs. The animal experiments conformed to the guidelines for the maintenance and handling of experimental animals established by the Tokyo University of Agriculture Ethics Committee (permission number: 060071).

2.3 Immunoblot analysis

To extract neutral salt-soluble collagen (tropocollagen) from the dermal skin, the skin was homogenized in physiological saline at 0°C, shaken for 20 h at 0°C, and finally centrifuged as described by Niedermüller *et al.* [15]. The supernatant (tropocollagen) was loaded and electrophoresed on a 6% w/v Tris-glycine polyacrylamide gel in SDS. After the electrophoresis, the proteins were transferred to a nitrocellulose membrane (Hybond-ECL, GE Healthcare) by using a transfer buffer, and the membrane was then blocked with PBS containing 1% w/v nonfat dried milk and 0.05% v/v Tween 20 for 1 h. The membrane was incubated with anti-rat type I collagen polyclonal antibody at 4°C overnight, washed five times with PBS containing 0.5% v/v Tween 20, and incubated with anti-rabbit IgG-horseradish peroxidase (1:2500 dilution in the blocking buffer) for 1 h. After washing the membrane five times with PBS containing 0.5% v/v Tween 20, the collagen was detected by using ECL Western Blotting Detection Reagents. The

Table 1. Composition and energy values of experimental diets

Ingredients (g/kg diet)	Groups					
	CO	Lard 5%	Lard 10%	Lard 15%	Lard 20%	Lard 25%
Casein	200.0	200.0	200.0	200.0	200.0	200.0
DL-Methionine	3.0	3.0	3.0	3.0	3.0	3.0
Sucrose	500.0	500.0	450.0	400.0	350.0	300.0
Cornstarch	150.0	150.0	150.0	150.0	150.0	150.0
Cellulose powder	50.0	50.0	50.0	50.0	50.0	50.0
Mineral mixture[a)]	35.0	35.0	35.0	35.0	35.0	35.0
Vitamin mixture[a)]	10.0	10.0	10.0	10.0	10.0	10.0
Choline bitartrate	2.0	2.0	2.0	2.0	2.0	2.0
Corn oil	50.0	–	–	–	–	–
Lard	–	50.0	100.0	150.0	200.0	250.0
% Total energy						
Carbohydrates	67	67	58	50	43	37
Fat	12	12	22	31	39	46
Protein	21	21	19	18	17	16
kJ/g diet						
Energy density	16	16	17	18	19	20

a) Based on AIN-76 mixture (Oriental Yeast Co., Tokyo).

amount of tropocollagen in the skin was assessed by analyzing the intensity of the collagen α-chain band that corresponds to a single-chain component by using LAS-3000 (Fujifilm, Tokyo). The protein level for each test group was expressed as a relative value to that of the control.

2.4 Quantification of hyaluronan

Skin samples were prepared as described previously by Oishi *et al.* [16]. Briefly, 2 cm^2 pieces of skin were defatted with acetone, dried, and weighed. The skin pieces were boiled for 20 min in 50 mM Tris/HCl (pH 7.8) buffer, and they were then subjected to proteolytic digestion with 1% w/v actinase E for a week at 40°C. Trichloroacetic acid was added to the samples at a final concentration of 10% w/v for deproteinization before the samples were centrifuged (3000 rpm, 4°C, 20 min). The supernatants thus obtained were neutralized with 10 N NaOH. Each supernatant was then concentrated and desalted with Centriplus YM-30, and treated with hyaluronidase (1 TRU/mL) in 500 μL of a 20 mM acetate buffer (pH 6.0) containing 0.15 M NaCl at 60°C for 18 h. The reaction was stopped by boiling for 10 min. After ultrafiltration with a Microcon YM-30 filter, the hyaluronan content was evaluated by measuring the amount of uronic acid in the filtrate, as described by Bitter *et al.* [17].

2.5 RNA extraction and quantitative PCR

Total RNA was extracted from the liver and skin by using the method reported by Chomczynski and Sacchi [18]. cDNA was prepared from 5 μg of DNase I-treated total RNA by reverse transcription, according to the manufacturer's instructions. Hybridization primers were synthesized by Applied Biosystems. The amplification products obtained were detected using a TaqMan Universal PCR Master Mix core reagent kit. Oligonucleotides that specifically hybridized to proximate regions of the target cDNA were prepared. The target genes were analyzed, and the sequences of the respective primers and probes are listed in Table 2. The amplification products of *TGF-β1* and *IGFBP-3* were detected using TaqMan Gene Expression Assays. The mRNA levels of *COL1A1, rhas2, rhas3, IGF-I, IGFBP-3,* and *TGF-β1* were measured by quantitative PCR using an ABI Prism 7300 apparatus (Applied Biosystems), and the levels were expressed as a relative value to that of β-actin. Amplifications were performed under the following conditions: 2 min at 50°C and 10 min at 95°C, followed by 50 cycles of 15 s at 95°C and 1 min at 60°C.

2.6 Analysis of serum adiponectin

The serum level of adiponectin was measured by using Mouse/rat adiponectin ELISA kit according the manufacturer's instructions.

2.7 Statistical analysis

Statistical analysis was performed by using the SPSS 15.0J software. The significance of the differences of the means among the six groups was assessed by Tukey's multiple comparison tests.

Table 2. Primer and probe sequences used for the quantification of gene expression

Target gene		Primer and probe sequences (5′–3′)	GeneBank accession number
Rat β-actin	Forward primer	CCCTGGCTCCTAGCACCAT	
	Reverse primer	GATAGAGCCACCAATCCACACA	V01217
	Probe	VIC-AGATCATTGCTCCTCCTGAGCGCAAGT-TAMRA	
Rat COL1A1	Forward primer	CGAAGGCAACAGTCGATTCAC	
	Reverse primer	TGACTGTCTTGCCCCAAGTTC	Z78279
	Probe	FAM-TGGATGGCTGCACGAGTCACACC-TAMRA	
Rat has2	Forward primer	CCAATGCAGTTTCGGTGATG	
	Reverse primer	ACTTGGACCGAGCCGTGTAT	AF008201
	Probe	FAM-AGCCCAGACTCAGTACCCTGTTGGTAAGGT-TAMRA	
Rat has3	Forward primer	CCTCATCGCCACAGTCATACAA	
	Reverse primer	CCACCAGCTGCACCGTTAGT	AF543196
	Probe	FAM-TGGCCGCATCTGGAACATTCTCC-TAMRA	
Rat IGF-I	Forward primer	CACAGGCTATGGCTCCAGCAT	
	Reverse primer	TCACAGCTCCGGAAGCAACA	M17335
	Probe	FAM-CCACAGACGGGCATTGTGGATGA-TAMRA	

Table 3. The effect of dietary fats on the energy intake and initial and final body weights in rats

Group	Energy intake	Initial body weight	Final body weight
	kJ/day	g	g
CO	381 ± 4^{a}	153 ± 1	373 ± 7
Lard 5%	389 ± 4^{a}	153 ± 2	380 ± 10
Lard 10%	414 ± 4^{b}	153 ± 2	390 ± 12
Lard 15%	427 ± 4^{b}	152 ± 2	407 ± 10
Lard 20%	448 ± 4^{c}	153 ± 2	409 ± 9
Lard 25%	456 ± 4^{c}	153 ± 2	417 ± 16

Values are means $\pm$ SE ($n = 5$). Values bearing different letters in the same column are significantly different at $p < 0.05$.

3 Results

3.1 Body weight and energy intake

We assessed the effects of an HF diet on body weight by using an animal model fed a high-calorie diet. The addition of lard to the diet increased the body weight and energy intake in a dose-dependent manner throughout the experimental period in the HF diet groups as compared with the CO group (Table 3).

3.2 Effects of HF diets on the level of type I tropocollagen and *COL1A1* mRNA in rat skin

Figure 1A shows the level of type I tropocollagen in the skin of the rats in the HF diet groups. The addition of lard reduced the level of type I tropocollagen in a dose-dependent manner, and the lard 15, 20, and 25% groups had significantly decreased protein levels as compared with the CO groups. Similarly, the addition of lard downregulated the expression of *COL1A1* mRNA in a dose-dependent manner, and the lard 20 and 25% groups showed significantly repressed transcription of the *COL1A1* gene as compared with the CO groups (Fig. 1B).

3.3 Effects of HF diets on the level of hyaluronan and *rhas2* and *rhas3* mRNA expression in rat skin

The effect of HF diets on the level of hyaluronan in skin was investigated (Fig. 2A). Hyaluronan levels were negatively correlated with the concentration of lard, and the levels were significantly low in the lard 10, 15, 20, and 25% groups as compared with the CO groups. Next, we investigated the mRNA levels of the two major HASs *rhas2* and *rhas3* (Figs. 2B and C). The mRNA levels of *rhas2* in the lard 20 and 25% groups were considerably lower than those in the CO group (Fig. 2B). In contrast, the mRNA level of *rhas3* was positively correlated with the concentration of lard, and the level was significantly increased in the lard 25% group as compared with the CO group (Fig. 2C).

3.4 The mRNA levels of *TGF-β1* in skin, and *IGF-I* and *IGFBP-3* in the liver of rats fed HF diets

To elucidate the mechanisms underlying the reduction in the skin levels of type I tropocollagen and hyaluronan, the

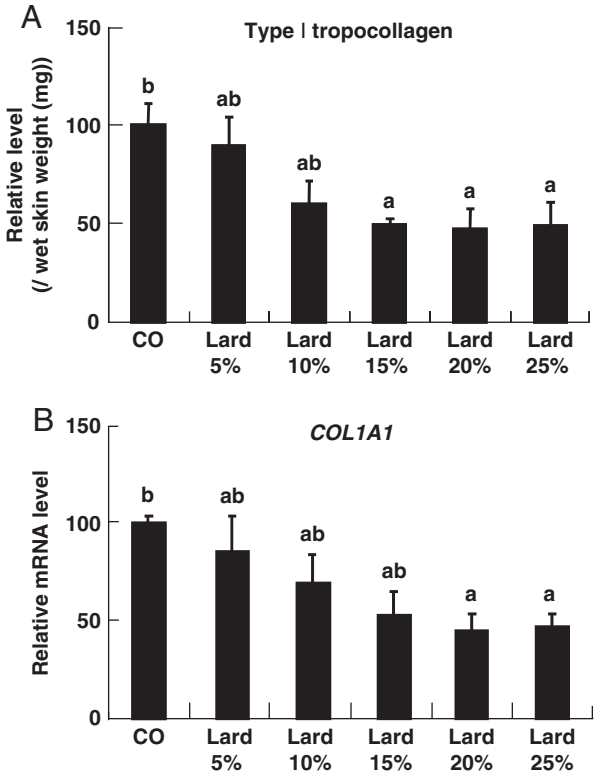

Figure 1. Effects of HF diets on the levels of type I tropocollagen and *COL1A1* mRNA in the dorsal skin of rats. Type I tropocollagen (A) in rat skin was quantified by western blotting. Variation in density was expressed as a fold change relative to the control in the blot. The mRNA level of *COL1A1* (B) in the rat skin was measured by quantitative PCR, and the values are expressed as a relative value to that of β-actin. Values are expressed as mean ± SE ($n = 5$). Bars without a common letter represent significant differences ($p < 0.05$).

effects of HF diets on the mRNA levels of *TGF-β1* in skin and *IGF-I* and *IGFBP-3* in the liver were investigated. The mRNA level of *TGF-β1* decreased in the lard groups, with a significant decrease in the lard 25% group (Fig. 3A). The mRNA level of *IGF-I* significantly decreased in all the test groups as compared with the CO group (Fig. 3B). The mRNA levels of *IGFBP-3* were substantially higher in all the test groups as compared with the CO group (Fig. 3C).

3.5 Effect of HF diets on the serum adiponectin concentration

Adiponectin promotes the syntheses of type I collagen and hyaluronan in human dermal fibroblasts [8]. Therefore, we examined the effect of HF diets on the concentration of serum adiponectin. The concentrations of serum adiponectin in the lard 20 and 25% groups were substantially lower than those in the other groups (Fig. 4).

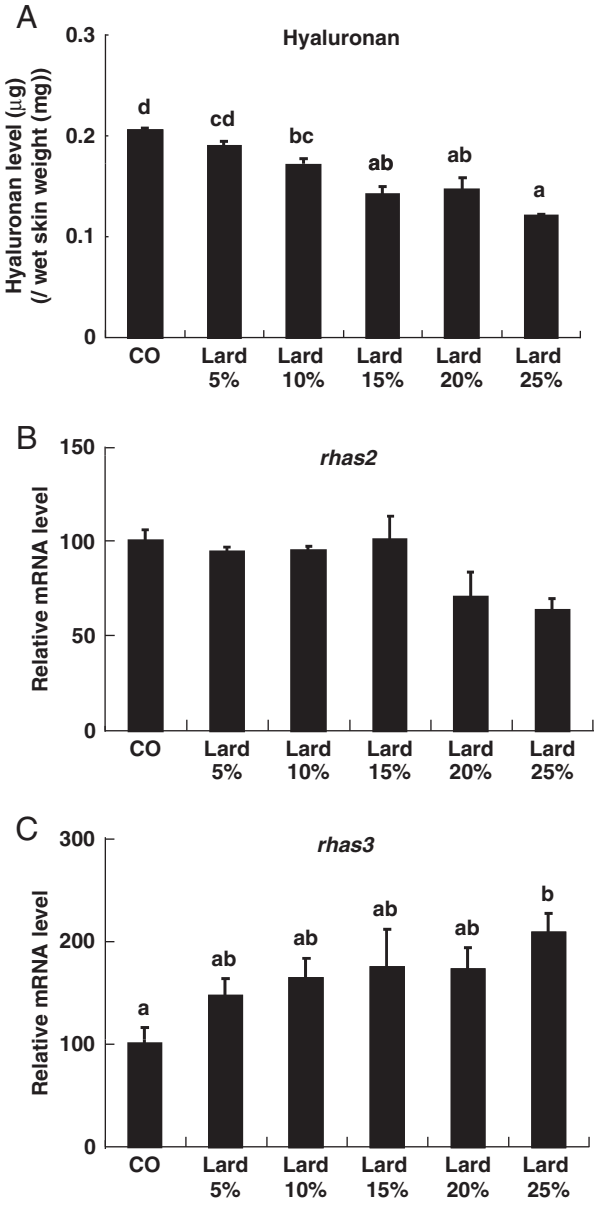

Figure 2. Effects of HF diets on the levels of hyaluronan and *rhas2* and *rhas3* mRNA in the dorsal skin of rats. The amount of hyaluronan (A) was measured by using Dische's carbazole method. The mRNA levels of *rhas2* (B) and *rhas3* (C) in the rat skin were measured by quantitative PCR and expressed as a relative value to that of β-actin. Values are given as mean ± SE ($n = 5$). Bars without a common letter represent significant differences ($p < 0.05$).

4 Discussion

The excessive consumption of HF diets by individuals remains one of the biggest problems in many countries and is likely to become more serious with the increase in population worldwide. Excessive fat intake causes not only lifestyle-related diseases but also skin-related diseases

including skin atrophy, the retardation of wound healing, and the deterioration of bedsores [5–7]. However, the molecular mechanism underlying the changes in skin function due to the consumption of HF diets remains unclear. Therefore, in the present study, we examined the changes in molecules related to skin function in rats fed HF diets.

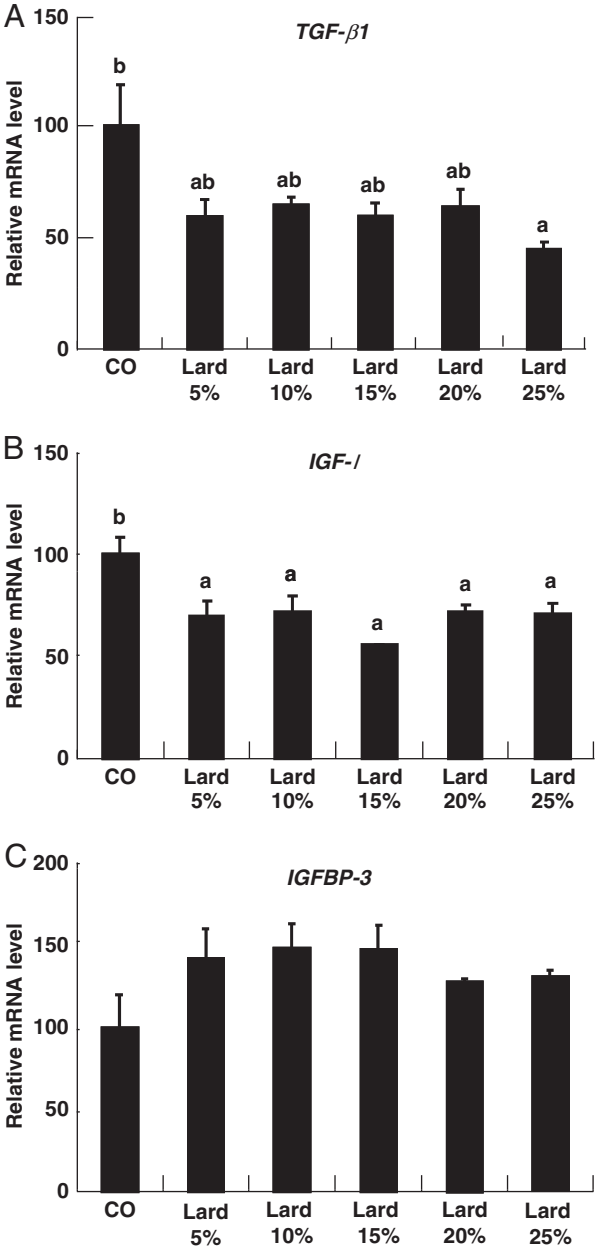

Figure 3. Effects of HF diets on the mRNA levels of *TGF-β1* in the skin and *IGF-I* and *IGFBP-3* in the liver of rats. The mRNA levels of *TGF-β1* in the rat skin (A), and *IGF-I* (B) and *IGFBP-3* (C) in the liver of rats were measured by quantitative PCR and expressed as a relative value to that of β-actin. Values are given as mean ± SE ($n = 5$). Bars without a common letter represent significant differences ($p < 0.05$).

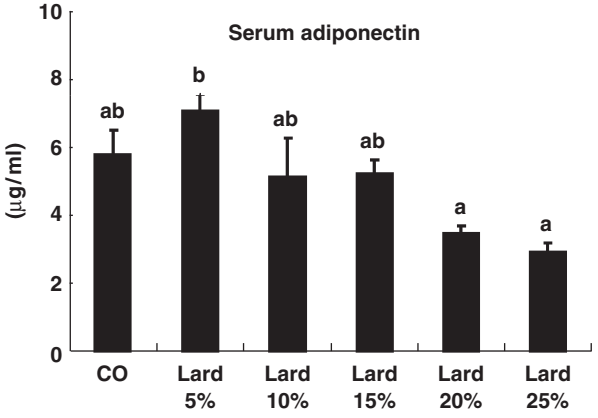

Figure 4. Effects of HF diets on the serum adiponectin concentration in rats. The serum adiponectin levels in rats were measured by ELISA. Values are given as mean ± SE ($n = 5$). Bars without a common letter represent significant differences ($p < 0.05$).

The HF diets decreased the skin levels of type I tropocollagen and *COL1A1* mRNA. These results indicate that the downregulation of type I collagen synthesis probably occurs at the transcriptional level (Figs. 1A and B). In addition, HF diets reduced the hyaluronan level in skin (Fig. 2A). Further, the skin mRNA level of *rhas2,* the major producer of hyaluronan in the dermis, was suppressed by HF diets (Fig. 2B). In contrast, the skin mRNA level of *rhas3*, the primary producer of hyaluronan in the epidermis, was significantly increased, and *rhas3* mRNA levels were positively correlated with the concentration of lard in the diet (Fig. 2C). Interestingly, Spicer and Tien [19] reported an increase in hyaluronan synthesis along with increases in *HAS2* transcripts in many cases. Averbeck *et al.* [20] have shown that *HAS2* and *HAS3* mRNAs were equivalently expressed in human skin. Furthermore, Itano *et al.* [21] reported that *HAS1* and *HAS2* had faster elongation rates than *HAS3*. Taken together, one reason for the reduction in the weight of hyaluronan may be that the suppression of *rhas2* had a greater effect than the increase of *rhas3*.

To clarify the mechanism underlying the reduction in type I tropocollagen and hyaluronan in the skin following the consumption of HF diets, we next determined the *TGF-β1*, IGF-I, and adiponectin levels. HF diets reduced the skin mRNA expression of *TGF-β1* (Fig. 3A), which enhances *COL1A1* and *rhas2* mRNA expression in human fibroblasts [22, 23] and decreases *rhas3* mRNA expression in human keratinocytes [24]. Presumably, reduced *TGF-β1* levels led to the repression of *COL1A1* and *rhas2* mRNA expression and upregulation of *rhas3* mRNA expression.

IGF-I is mainly produced in the liver and enhances *COL1A1, rhas2,* and *TGF-β1* mRNA expression in fibroblasts [25–27]. The present study showed that HF diets decreased the hepatic mRNA level of *IGF-I* (Fig. 3A). Chan *et al.* [28] also reported that the mRNA level of *IGF-I* in the liver was decreased in obese Zucker rats, but the

mechanism underlying this reduction has not been fully characterized. In addition, our study showed that HF diets increased the mRNA level of *IGFBP-3*, which inhibits IGF-I bioavailability in serum (Figs. 3B–C) [29–31]. Taken together, the reductions in IGF-I level and IGF-I activity (*via* increases in the IGFBP-3 level) following the consumption of HF diets would decrease the mRNA levels of *COL1A1* and *rhas2* directly and/or by lowering *TGF-β1* levels. Such a decrease would lead to a reduction in the levels of type I tropocollagen and hyaluronan in the skin. However, further studies are required to determine the levels of free IGF-I and other IGFBPs in serum.

Additionally, the mRNA levels of *TGF-β1* and *IGF-I* were lower in the lard 5% group than in the control (corn oil 5%) group; this finding may be attributed to the differences in the components of corn oil and lard, such as vitamin E content and fatty acid composition. Some studies have shown that the high concentration of vitamin E contained in corn oil increased *IGF-I* mRNA expression in the bones of mice [32], and dietary olive oil, which is rich in oleic acid suppressed *TGF-β1* mRNA expression in the liver [33]. Indeed, the vitamin E content of lard is lower than that of corn oil. Moreover, the level of oleic acid in lard is higher than that in corn oil. It is likely that these factors were responsible for the differences in the levels of *TGF-β1* and *IGF-I* expression between the CO and lard 5% groups.

Adiponectin is one of the many adipocytokines secreted by the adipose tissue. A significant negative correlation exists between serum adiponectin concentration and body fat mass, and adiponectin concentration is decreased following the consumption of an HF diet [4, 34]. The adipocytokine has been shown to promote the syntheses of type I collagen and hyaluronan together with the upregulation of *HAS2* gene expression in human dermal fibroblasts [8]. Kawai *et al.* [35] have shown the possibility that adiponectin improved the impaired wound healing process seen in patients with diabetes, being associated with an increase in the *TGF-β1* gene expression in human keratinocytes. Sugihara *et al.* [36] have reported that the fat cells inhibited the proliferation of dermal fibroblasts using a skin system reconstructed with rat skin cells and fat cells in 3-D collagen gels and that the cytokines derived from adipocytes might elicit this inhibitory effect. These studies show the important roles of adiponectin in skin functions. In the present study (Fig. 4), the concentration of serum adiponectin decreased in rats fed a diet with HF content. Therefore, we propose that the reduction in the serum concentration of adiponectin caused by HF diets triggers the reduction in the skin levels of type I collagen and hyaluronan and leads to the decline in skin function. In addition, some researchers have reported that the interaction of adiponectin with AdipoR (adiponectin receptor)1 induces the synthesis of type I collagen in human osteoblasts and the activates p38 MAPK, which promotes *COL1A1* gene expression in cardiac fibroblasts [37, 38]. We observed by RT-PCR analysis that the *AdipoR1* and *AdipoR2* genes were expressed in rat skin (data not shown). Based on these findings, it is likely that adiponectin influences the syntheses of type I collagen and hyaluronan in the skin *via* endocrine action through the AdipoRs. However, some aspects of the relation between serum adiponectin levels and type I collagen and hyaluronan are unclear, and the relation between adiponectin and the other molecules involved in skin function, including rhas3, *TGF-β1*, and IGF-I, is still not fully understood.

In summary, we have shown that HF diets reduce the levels of type I tropocollagen and hyaluronan in the skin by decreasing the levels of *TGF-β1*, IGF-I, and adiponectin. At present, the energy from lipid intake accounts for a substantial percentage of total energy intake. In America, the current daily lipid intake (34–37% of total energy) exceeds the US Dietary Guideline recommendation of 30% energy from daily fat intake [39]. In Japan, although the total energy intake has not changed during the past 50 years, the fat intake has increased 3.8-fold [40]. Our study suggests that such dietary patterns may lead to skin dysfunction and a wide range of skin problems, including delayed wound healing and exacerbation of bedsores [5–7]. In addition, it has been shown that the reduction in hyaluronan decreases the activity of langerhans cells in the skin, thereby weakening the immunological state of skin [41], and that wound healing is delayed in overweight individuals [42]. We hope that the present study will contribute to the elucidation of the mechanisms underlying the effects of HF diets on the skin.

The authors have declared no conflict of interest.

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