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Caloric restriction inhibits up-regulation of inflammatory cytokines and TNF-α, and activates IL-10 and haptoglobin in the plasma of streptozotocin-induced diabetic rats

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Abstract

Diabetes mellitus is a significant risk factor for cardiovascular diseases, and low-grade systemic inflammation, mediated by oxidative stress, may play a central role. Caloric restriction (CR) has been reported to be effective in reducing oxidative stress during diabetes and moderating the expression of some markers of inflammation that are up-regulated during aging. Forty male Wistar rats were randomly divided into four groups: nondiabetic feeding ad libitum and under CR, and diabetic feeding ad libitum and under CR. The animals were subjected to 30% CR and ad libitum feeding for 9 weeks before the induction of diabetes by intraperitoneal injection with 35 mg/kg body weight streptozotocin. The inflammatory cytokines [interleukin (IL)-1β, IL-4 and IL-6] and tumor necrosis factor α up-regulated in diabetes were found to be significantly depressed by CR, whereas the antiinflammatory mediators, haptoglobin and IL-10 levels, were increased. These results indicated that CR could prevent diabetic complications through suppression of inflammatory responses.

Keywords: Inflammation; Diabetes; Caloric restriction; Interleukins; TNF-α; Haptoglobin

1. Introduction

Inflammation is one of the major risk factors for diabetic complications, especially atherosclerosis [1,2]. Low-grade systemic inflammation mediated by oxidative stress [3,4] has been reported to play a central role in both diseases [5]. Excessive food intake has been reported to generate oxidative stress [6], which stimulates proinflammatory mediators [7,8], leading to the development of insulin resistance and type II diabetes [9]. These proinflammatory mediators, including plasma interleukin (IL)-4, IL-6, and tumor necrosis factor α (TNF-α), are elevated in diabetic states [10,11]. It is hypothesized that the release of these mediators is induced by high glucose concentration and mediated by oxidative stress [7]. Therefore, targeting inflammation seems an attractive option/strategy for the treatment of insulin resistance, and this could possibly aid either in delaying the onset or ameliorating the effects of diabetes.

Previous studies in our laboratory indicated that caloric restriction (CR) improved glycemic control and reduced oxidative stress and lipid peroxidation, as measured by malondialdehyde levels in streptozotocin (STZ)-induced diabetic rats [6]. Caloric restriction has also been reported to improve glycemic homeostasis [12–15], reduce levels of oxidative stress and lipid peroxidation [6,12,13,16], and also reduce inflammatory processes that contribute to atherosclerosis, as indicated by reduced levels of leukocytes and TNF-α during aging [17,18].

No study has addressed the impact of dietary CR on modification of risk factors for cardiovascular complications in the plasma of STZ-induced diabetic rats. Therefore, the present study was designed to examine the antiinflammatory effects of CR on plasma levels of haptoglobin, TNF-α, IL-1β, IL-4, IL-6 and IL-10. This is part of an ongoing research in our laboratory geared toward using lifestyle changes (CR) as therapeutic intervention for attenuating the deleterious effects of diabetes.

2. Methods and materials

2.1. Experimental animals

Forty 3-month-old male Wistar rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 250–275 g were used

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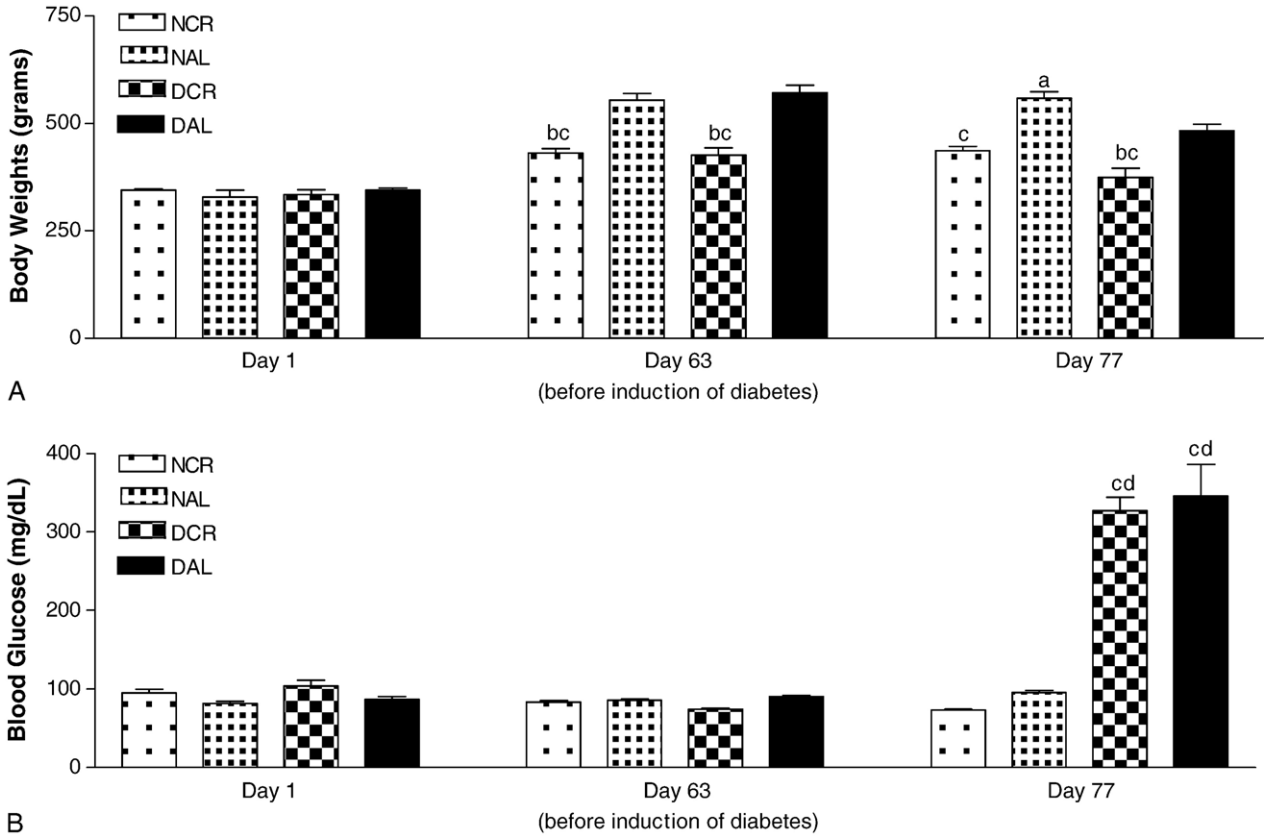

Fig. 1. The effects of dietary CR on body weights (panel A) and blood glucose levels (panel B) on days 1, 63 and 77 in the plasma of DCR, DAL, NCR and NAL rats. Values are mean±S.E.M.; $n=10$. [a]$P<.05$ as compared with diabetic rats feeding ad libitum. [b]$P<.001$ as compared with diabetic rats feeding ad libitum. [c]$P<.001$ as compared with nondiabetic rats feeding ad libitum. [d]$P<.001$ as compared with nondiabetic rats under CR.

for this study. The animals were housed singly for caloric restricted rats and doubly for the ad libitum fed rats in metabolic cages in the Animal Care Facility at the Florida A&M University, Tallahassee, FL, under controlled environmental conditions of temperature (68–72°F) and relative humidity (50±5%) and a 12-h light/dark cycle. The experimental animals were allowed to acclimatize for 7 days. Animals were fed commercial rat feed (19.92% protein, 5.67% fat, 4.37% ash, 53.66% nitrogen-free extract and 2.90% linoleic acid; Harland Teklad, Madison, WI). The experimental protocols used in this study were in accordance with the guidelines of the Animal Care and Use Committee (ACUC) of the Florida A&M University.

2.2. Experimental design

After acclimatization, the animals were randomly divided into 2 groups (caloric restricted and ad libitum) of 20 animals each. Caloric restriction was accomplished by 10% reduction in the daily food intake every 5 days until a 30% reduction was achieved. The feeding experiment was continued for 9 weeks (63 days), during which daily food intake as well as weekly body weights and blood glucose concentrations (LifeScan, Milpitas, CA) were monitored. On day 64, the animals were divided into subgroups: the 20 animals were divided as 10 diabetic and 10 nondiabetic caloric restricted (DCR and NCR, respectively) animals, and the other 20 were divided as 10 diabetic and 10 nondiabetic ad libitum fed (DAL and NAL, respectively) animals. These experimental animals were subjected to a 16-h fast, and diabetes was induced in 20 rats (10 DCR and 10 DAL rats) with STZ (35 mg/kg body weight dissolved in 0.01 mol/L citrate buffer, pH 4.5) intraperitoneally to obtain type 2 diabetic rats [19]. The NCR and NAL rats received only buffer. After 1 week, diabetes was confirmed with fasting blood glucose levels >200 mg/dl in the STZ-treated rats [6]. Two weeks after the administration of STZ, blood was collected from the hearts of animals by cardiac puncture prior to killing, placed in EDTA vacutainer tubes, and centrifuged at 4000×g at 4°C for 15 min and stored at −80°C until analysis.

2.3. Biochemical analysis

Blood was used for assaying blood glucose using OneTouch Ultra blood glucose monitoring system (LifeScan). The levels of haptoglobin, TNF-α, IL-1β, IL-4, IL-6 and IL-10 in the plasma were measured using solid-phase ELISA kits (BioSource International, Camarillo, CA) and Biorad Lumimark Plus plate reader (Biorad, Hercules, CA). This was performed by binding the antigen to the immobilized antibody on one site and to the solution phase

biotinylated antibody. The excess second antibody was removed, and streptavidin–peroxidase was added, which binds to the biotinylated antibody to complete the four-member sandwich. After a series of incubation and washing to remove all unbound enzyme, a substrate solution was added, which produced a color whose intensity was directly proportional to the concentration of the proinflammatory biomarker. All assays were carried out in triplicates. The concentrations were expressed as picograms of cytokines per milligram of protein per gram of tissue.

2.4. Determination of body weights

Weekly body weights of the experimental animals were taken to ensure good health in compliance with the university's ACUC guidelines. For experimental purposes, only the weights on day 1 before CR, day 63 before the induction of diabetes and day 77, the end of the study, were used for analysis.

2.5. Statistical analysis

The results were analyzed for statistical significance by one-way ANOVA test and Tukey's multicomparison post-test using GraphPad Prism computer software package version 3.0 (GraphPad Software, San Diego, CA). All data were expressed as mean±S.E.M., $n=10$. Differences between groups were considered significant at $P<.001$, $P<.01$ and $P<.05$.

3. Results

3.1. Body weight and blood glucose levels

No differences were found in the body weights of the experimental animals at the start of the experiment (Fig. 1A). However, CR was able to reduce the body weights of the experimental animals on day 63 before the induction of diabetes. On day 77, the body weights of the diabetic rats decreased slightly when compared with their values on day 63. No change was observed in the body weights of the nondiabetic animals on both days. The blood glucose levels are represented in Fig. 1B. The results indicated that no differences were observed on days 1 and 63 in all the experimental animals. However, with the induction of diabetes, the blood glucose levels increased significantly ($P<.001$) in the diabetic rats. Caloric restriction was only able to slightly reduce the glucose concentration in the DCR group when compared with the DAL group.

3.2. Plasma inflammatory markers

The plasma haptoglobin levels are shown in Fig. 2A. The result indicated that CR was able to significantly increase these levels in experimental rats. The level in NAL group was more depressed than that obtained for the DAL group. The TNF-α concentration (Fig. 2B) was found to be highly elevated in nondiabetic rats feeding ad libitum, though no significant difference was found between the level in NAL

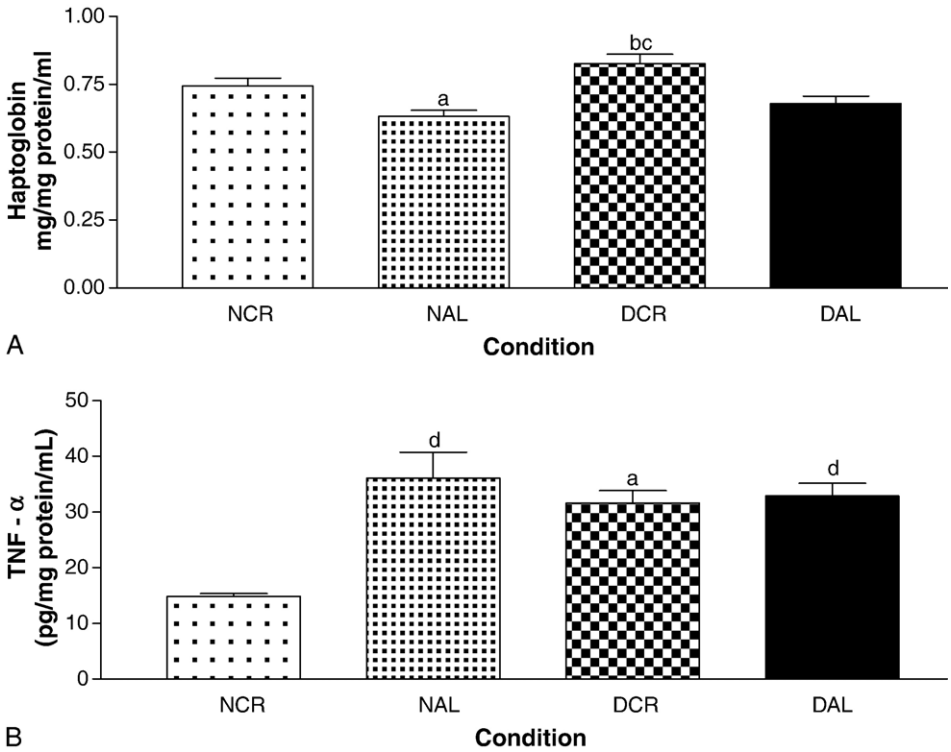

Fig. 2. The effects of dietary CR on haptoglobin (panel A) and TNF-α (panel B) in the plasma of DCR, DAL, NCR and NAL rats. Values are mean±S.E.M., $n=10$. [a]$P<.05$ as compared with nondiabetic rats under CR. [b]$P<.01$ as compared with nondiabetic rats feeding ad libitum. [c]$P<.05$ as compared with diabetic rats feeding ad libitum. [d]$P<.001$ as compared with nondiabetic rats under CR.

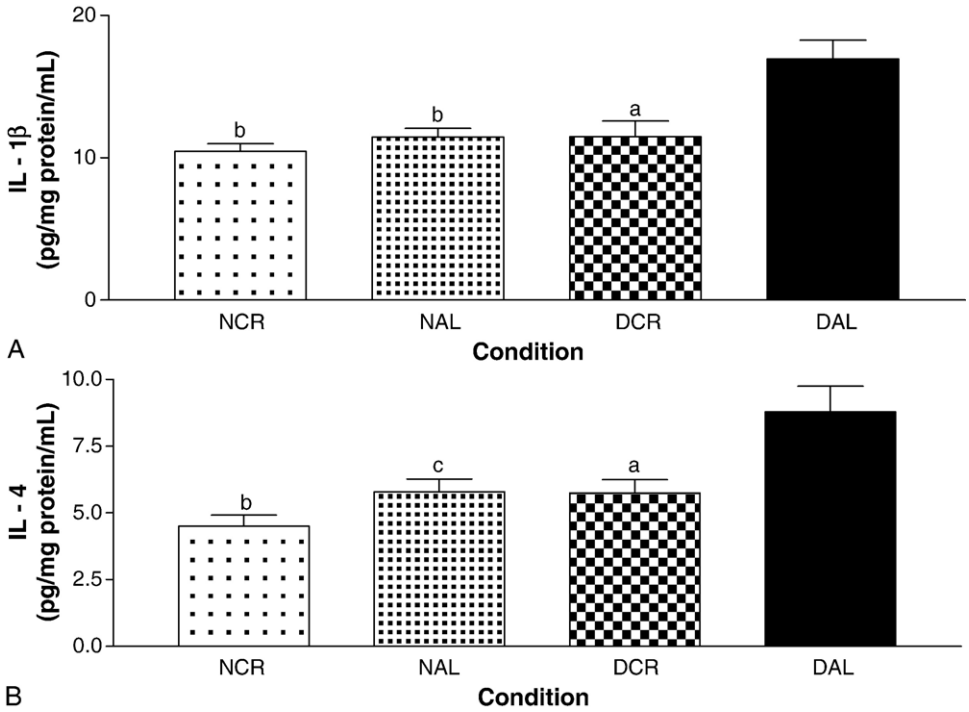

Fig. 3. The effects of dietary CR on IL-1β (panel A) and IL-4 (panel B) in the plasma of DCR, DAL, NCR and NAL rats. Values are mean±S.E.M., $n=10$. [a]$P<.05$ as compared with diabetic rats feeding ad libitum. [b]$P<.001$ as compared with diabetic rats feeding ad libitum. [c]$P<.01$ as compared with diabetic rats feeding ad libitum.

group and the diabetic groups. However, CR was found to significantly ($P<.001$) and nonsignificantly reduce the TNF-α levels in nondiabetic and diabetic rats, respectively.

The results in Fig. 3A showed the plasma concentration of IL-1β in the experimental rats. No significant difference was observed in all the experimental animals, except in DAL

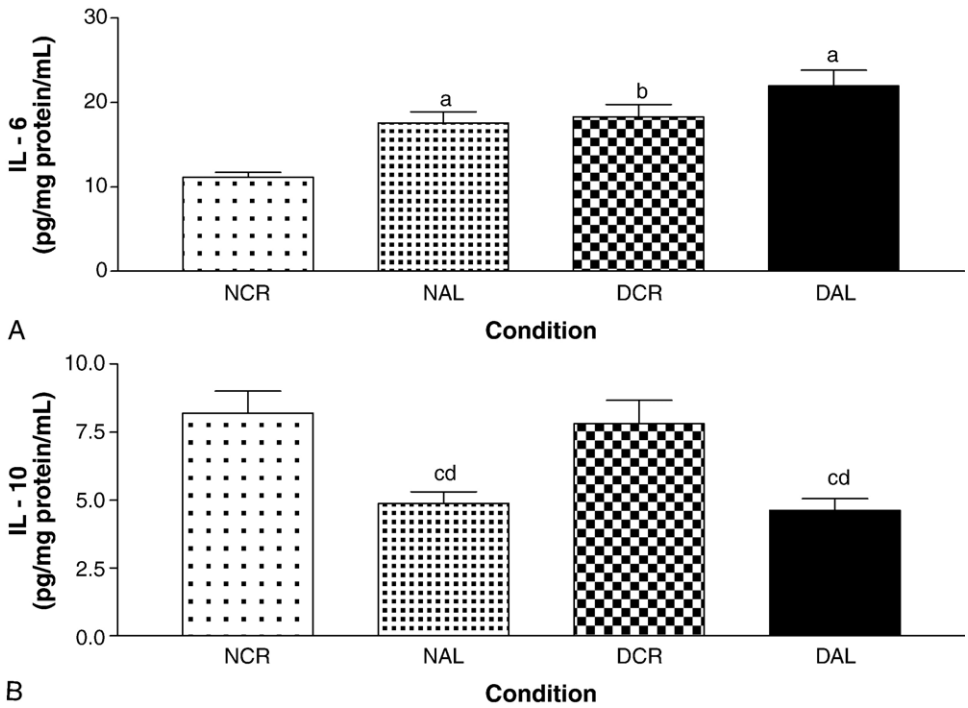

Fig. 4. The effects of dietary CR on IL-6 (panel A) and IL-10 (panel B) in the plasma of DCR, DAL, NCR and NAL rats. Values are mean±S.E.M., $n=10$. [a]$P<.001$ as compared with nondiabetic rats under CR. [b]$P<.05$ as compared with nondiabetic rats under CR. [c]$P<.01$ as compared with nondiabetic rats under CR. [d]$P<.001$ as compared with diabetic rats under CR.

group where it increased significantly ($P<.01$). The IL-4 levels (Fig. 3B) were found to be significantly elevated in diabetic rats fed ad libitum when compared with the other experimental animals. There were no significant differences among the NCR, NAL and DCR groups, though the NCR group had slightly depressed levels. Fig. 4A showed that CR was able to reduce the IL-6 concentration in the experimental rats when compared with their counterparts. The NCR levels were significantly reduced when compared with the other groups. The IL-10 levels shown in Fig. 4B were significantly increased in experimental animals under CR. However, there were no significant differences within the groups fed ad libitum or under CR. The results indicate that there is a correlation in the pattern of up-regulation or down-regulation of these mediators by CR in consonant with their physiological activities during diabetes.

4. Discussion

In this study, we found that the body weights of the experimental animals subjected under CR were significantly reduced when compared with their counterparts fed ad libitum before the induction of diabetes on day 63. However, on day 77, there was a drop in body weights of the diabetic animals compared with the nondiabetic groups. These results suggest that the drop in body weights of these diabetic animals could be a result of the observed less caloric intake by these animals and the physiological adaptations occurring at the onset of diabetes. The significant increase in body weight in NAL group was due to excess food intake, which is known to generate oxidative stress [6] and in turn stimulate proinflammatory mediators [8]. This could explain the elevated levels of these proinflammatory mediators in NAL rats and the subsequent pathological findings. The blood glucose levels in the diabetic rats were significantly elevated compared with the levels in nondiabetic animals, proving that these animals were hyperglycemic. There was only a slight reduction in glucose levels in the DCR animals, possibly because measurement was carried out at the onset of diabetes.

There is ample evidence that subclinical inflammation is a risk factor for insulin resistance, type 2 diabetes and cardiovascular disease [20–23]. It is postulated that chronically elevated lipid and glucose levels present in obesity and diabetes pose a permanent stress on the vascular endothelium that is aggravated by inflammatory proteins and resulting in the development of atherosclerosis [9]. In this study, we measured both the inflammatory and antiinflammatory biomarkers that are known to mediate in the inflammatory response. Haptoglobin, the major hemoglobin binding protein in the serum, is known to inhibit hemoglobin-stimulated oxidative tissue damage [24,25] and prostaglandin synthesis, thus, possessing antiinflammatory properties. Caloric restriction was found to significantly elevate the serum levels of haptoglobin in the experimental animals. These elevated levels would help prevent oxidative stress known to be exacerbated during diabetes. This defense mechanism could well be one of the various responses by CR in the modulation of the effects of diabetes.

Plasma IL-6 and TNF-α were elevated in the obese and in type 2 diabetes [26,27]. Tumor necrosis factor α, generated during the systemic inflammatory response, was involved in the pathophysiology of hypertension and dyslipidemia associated with obesity and insulin resistance [28]. The TNF-α levels, which were usually up-regulated in type 2 diabetes [26], were found to be depressed significantly in nondiabetic rats and nonsignificantly in diabetic rats under CR. The nonsignificant decrease in diabetic rats under CR could be due to the stage of the disease that was at the onset of diabetes, where the effect of CR had not been fully exercised. There was an observable muscle wasting in the diabetic rats, but it was much more intense in the nondiabetic rats feeding ad libitum. This could be attributed to the elevated levels of TNF-α and other circulating cytokines, which were implicated in the activation of apoptotic mechanisms and/or enhanced myofibrillar protein degradation of the muscle tissue [29–33]. Interleukin 6 levels had been shown to be elevated during acute phase response (APR), which could be triggered by diabetes resulting in the release of effector molecules that might cause endothelial dysfunction leading to atherosclerosis [34,35]. Though APR was a beneficial short-term response to inflammation, it could be harmful when chronically activated, as in obesity and type 2 diabetes. Mohamed-Ali et al. [36,37] reported that approximately 25–30% of serum IL-6 originated from adipose tissue, and that secretion of IL-6 from subcutaneous fat was in proportion to fat mass. The IL-6 levels in the experimental animals were found to be down-regulated by CR. Caloric restriction significantly depressed both IL-6 and TNF-α concentrations in the nondiabetic rats. This correlation could be expected because TNF-α induced IL-6 production [38], which in turn regulated the production of CRP in the liver [39]. Tchernof et al. [40] demonstrated that a fall in CRP levels in postmenopausal women was correlated with changes in body weight and fat mass. Though CRP levels were not measured in this study, IL-6 was known to induce the production of CRP, and more so, the fall in IL-6 and TNF-α levels in rats under CR correlated with the reduction in body weight. Therefore, CR resulting in weight loss and reduction of IL-6 and TNF-α levels in experimental animals could well dampen the inflammatory responses in these rats. Caloric restriction has been found in various studies to reduce the inflammatory response in rat myocardium [41] and during allergic responses [42]. Frame et al. [43] suggested that the reduced inflammatory response might account for some of the enhanced longevity in caloric restricted rats.

The IL-1β, like the TNF-α and IL-6, is produced and secreted by adipose tissue and is proinflammatory [44]. The trio has been found to be elevated during aging and diabetes [45]. They are known to influence β-cells and to be toxic at

relatively high concentrations and have all been implicated in type 2 diabetes [46]. The IL-1β levels in the diabetic rats fed ad libitum was significantly elevated. There was no significant difference among the NCR, NAL and DCR groups. However, CR was found to reduce the levels of IL-1β in diabetic animals. These reductions by CR could mean that these down-regulations might in part be due to weight loss/less fat mass where these proinflammatory mediators are produced.

Interleukin 4 is an antiinflammatory cytokine [44,47], but very high IL-4 levels in the serum could possibly cause the progression of diabetes [48]. The Th1 cells from $CD4^+$ T cells produce IL-2, whereas the Th2 cells produce IL-4 and IL-10. Both the IL-4 and IL-10 play dominant roles in several immune responses. Interleukin 10 was reported to suppress spontaneous diabetes in NOD mice [49]. The IL-4 concentrations did not show any significant changes in all the experimental animals, except in the DAL group that was significantly elevated. This significant increase in the DAL rats could mean overexpression of the IL-4 in these rats, which might be toxic and lead to complications. The results also indicated that CR elevated the IL-10 levels in the experimental rats. Interleukin 10 has been reported to suppress the production of the proinflammatory cytokines and costimulates the proliferation and differentiation of β-cells for effective defense system [49,50].

In conclusion, our studies indicate that CR significantly reduced body weight, IL-1β and IL-4, and increased haptoglobin and IL-10 in diabetic rats. Caloric restriction also produced subtle changes in the blood glucose levels, TNF-α and IL-6 concentrations in diabetic rats. These results indicate that CR can improve endothelial function in diabetic rats, possibly through the reduction in body weight resulting in reduction in fat mass and concomitant reduction in the production of the proinflammatory markers. However, it is worthy to note that the nondiabetic rats fed ad libitum had elevated proinflammatory mediator levels, and this could be attributed to their high body weights due to observed excessive fat mass.

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