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Original Article

Early consumption of high-fat diet worsens renal damage in spontaneously hypertensive rats in adulthood

Renata Oliveira Pereira[1,2], Cynthia Rodrigues Muller[3], Nilberto Robson Falcão de Nascimento[4], Manassés Claudino Fonteles[2,4], Fabiana Sant'Anna Evangelista[5], Patricia Fiorino[2], Vera Farah[1,2]

[1]Translational Medicine Division, Department of Medicine, Federal University of Sao Paulo, Sao Paulo, SP, Brazil; [2]Renal, Cardiovascular and Metabolic Physiopharmacology Laboratory, Health and Biological Science Center, Mackenzie Presbyterian University, Sao Paulo, SP, Brazil; [3]Department of Bioengineering, University of San Diego, San Diego, CA, USA; [4]Superior Institute of Biomedical Sciences, Ceara State University, Fortaleza, CE, Brazil; [5]School of Arts, Sciences and Humanities, University of Sao Paulo, Sao Paulo, SP, Brazil

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Abstract: The association between hypertension and obesity has been shown to be an important cause of kidney disease. We aimed to investigate the impact of a high-fat diet (HFD) administered in spontaneously hypertensive rats (SHR) after weaning in renal morphology and functional parameters. Male post-weaned SHR were divided into two groups: standard control diet (CD) (3% lipids; n = 8) or HFD (30% lipids; n = 8) during 8 weeks. The group HFD showed an increase in serum triglycerides (HFD: 96 ± 7 vs. CD: 33 ± 2 mg/dL) and glucose intolerance (HFD: 185 ± 7 vs. CD: 149 ± 4 mg/dL/min). Moreover, the HFD also showed an increase in almost 90% of the periepididymal and retroperitoneal adiposity. There was no difference in arterial blood pressure between groups. Renal morphofunctional parameters were decreased in HFD group for glomerular tuft area and diameter (4733 ± 65 μm^2 and 82 ± 1 μm, respectively) when compared with CD group (5289 ± 171 μm^2 and 88 ± 2 μm, respectively). HFD also showed a decrease of 50% of the renal function, which was associated with higher renal extracellular matrix and lipid deposition. Therefore, our data suggest that HFD since early period of life may contribute to renal damage in adults with hypertension, and this impairment can be associated with increased renal lipid accumulation.

Keywords: High-fat diet, SHR, kidney

Introduction

Arterial hypertension is one of the leading causes of death around the world [1]. The prevalence of arterial hypertension by the year 2000 was over 25% of adult population and the estimative for the year 2025 is around 30% [2]. Hypertension is often asymptomatic, and its progression is strongly associated with complications in target organs, such as the brain, the heart and especially the kidneys [3].

Hypertensive patients have a major risk to develop chronic kidney disease (CKD) [4-6]. The persistence of high blood pressure causes structural alterations in renal arteries and arterioles, glomerular and tubulointerstitial damage, and renal extracellular matrix deposition [7]. Worldwide, more than one million people die annually due to CKD [8]. The consumption of high-fat (HF) diets is increasing globally [9] and is also a major risk factor for the development of renal dysfunction [10].

HF diets induce adipocytes hypertrophy and obesity, which leads to an increase in the endocrine and inflammatory activity of the adipose tissue. This culminates with high levels of adipokines in the systemic circulation, such as leptin, angiotensin II, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) [11]. In the kidney, these adipokines can induce oxidative stress, inflammation and fibrosis, contributing to the development and progression of the kidney disease [12]. Thus, overweight or obese hypertensive patients have a higher risk

of developing CKD and present a worse prognosis [5].

It has been shown that HF diet increases the deposition of lipids not only into adipose tissue but also into non-adipose tissues. The excessive lipid accumulation leads to several deleterious effects on tissues and organs, which is called lipotoxicity [13]. In the kidney, the deposition of lipid droplets can promote mitochondrial dysfunction, endoplasmic reticulum stress, tubulointerstitial fibrosis, apoptosis and renal dysfunction [14]. As HF diet plays a significant role in determining adiposity and lipotoxicity, one of the possible mechanisms mediating this increased risk of CKD in hypertensive patients can be abnormal renal lipid deposition. Previous research of our group has demonstrated that mice fed a cafeteria diet showed excessive renal lipid deposition, which was associated with glomerular hyperfiltration and morphological damage [15]. Moreover, our group has recently shown that high-fat diet since post-weaning induced renal lipid accumulation, inflammation, glomeruli retraction and renal dysfunction in adult Wistar rats [16].

The consumption of HF diets starts early in life, especially in developed and developing countries [17]. The early consumption of fat requires special attention since hypercaloric dietary habits in childhood predicts the development of several metabolic disorders in adulthood such as type 2 diabetes, obesity and cardiovascular disease [18-20]. We previously demonstrated that HF diet consumption during early period of life, increased white adipose tissue depots and mean arterial pressure in normotensive Wistar rats [21]. These results elucidated that early cardiometabolic damages induced by HF diet can lead to the development of arterial hypertension and increase cardiovascular risk in adulthood.

The association between arterial hypertension and renal dysfunction is well established in the literature. However, the role of early intake of HF diet on main renal morphofunctional parameters of hypertensive patients is not known. Therefore, the aim of this study was to investigate the impact of a HF diet administered since post-weaning on renal morphology and functional parameters of adult spontaneously hypertensive rats (SHR). Our hypothesis is that the consumption of HF diet since post-weaning worsens renal damage in hypertensive animals in adulthood and this response is associated with excessive renal lipid accumulation.

Material and methods

Animals

Experiments were performed using male post-weaned (21 days old) SHR, weighing between 40 and 50 g, obtained from the Central Animal Facility of Mackenzie Presbyterian University (Sao Paulo). The animals were housed in standard cages with free access to food and water and maintained in the Central Animal Facility of Mackenzie Presbyterian University under the same housing conditions (12-h light/12-h dark cycle, temperature 23 ± 2°C). The animals were randomly divided into two groups (12-16 animals per group), control diet (CD) and high-fat diet (HFD), and followed for eight weeks.

Diets

The high-fat diet used in the present study was previously developed in our laboratory and it was prepared by mixing the standard diet (400 g) with unsalted butter (200 g) (saturated fat). The high-fat diet produced contained 30% of fat, 23% of carbohydrates and 19% of proteins [21]. The standard diet contained 3% of fat, 55% of carbohydrate and 22% of proteins (Nuvilab®, Paraná, Brazil). Caloric densities of high-fat diet and standard diet were respectively 381 kcal/100 g and 257 kcal/100 g. All procedures and protocols used were in accordance with the Guidelines for Ethical Care of the Experimental Animals and were approved by the Ethics Committee of Mackenzie Presbyterian University (Protocol: 127/08/2015) and by the Ethics Committee of Federal University of Sao Paulo (UNIFESP) (Protocol: 7005180516).

Glucose tolerance test and metabolic cage

The glucose tolerance test (GTT) was performed during the 7th week of protocol, in awake animals after 8-h fasting. An intraperitoneal glucose load (1.5 g/kg) was injected and the blood glucose levels concentration were determined using a glucometer (AccuChek Advantage Roche Diagnostics®). Blood samples were taken from a cut made on the tip of the tail at baseline and at 15, 30, 60, 90 and 120 min-

utes. The areas under the curves (AUC) were calculated as previously reported [22].

At the 8th week of protocol, part of the animals (n = 6) was placed in individual metabolic cages during 24-h for adaptation following 24-h to evaluate food intake and urine volume. Urine samples were collected and stored for biochemical analysis.

Cardiovascular measurements

After 8 weeks of experimental protocol, the animals that were not placed in the metabolic cages (n = 6) were anesthetized with Ketamine (Dopalen-80 mg/kg, i.p.) and Xylazine (Anasedan-12 mg/kg, ip) and submitted to surgery for catheterization of the femoral artery and vein. After 24 h of surgery, with the animals awake and moving freely, the arterial cannula was connected to a strain gauge transducer (Hewlett-Packard 1280, EUA). The arterial pressure signals were recorded for 30 minutes, starting just after the stabilization of the exploratory activity of the animal.

Animals were conscious and moved freely during recording. The arterial pressure signal was coupled to an amplifier (GPA-4 model 2, Stemtech Inc.) connected to a 16-channel analog-to-digital interface, and continuously sampled (2 kHz) on an IBM/PC (T23, IBM Thinkpad, Inc). Beat-to-beat values of mean arterial pressure was determined and heart rate was calculated using the software application WinDaq (DataQ Instruments, Inc., USA) [23].

Euthanasia and biochemical measurements

The animals were killed by an intraperitoneal overdose of anesthetic (Ketamine 160 mg/kg; Xylazine 24 mg/kg) for tissue collection. Visceral white adipose tissue (periepididymal and retroperitoneal fat pad) was harvested and weighed. The right Kidney was harvested and stored at -80°C. The left kidney was excised, part was fixed with 4% buffered formaldehyde and part was stored at -80°C, covered with OCT compound (Tissue-Tek, Sakura Finetek USA, Inc., Torrance, CA). Blood samples were taken from the cava vena, centrifuged during 15 min (4°C, 10000 rpm) and serum was stored at -20°C.

The urine samples were used for analysis of creatinine and total protein concentrations. Serum samples were used for measurements of triglycerides, cholesterol, total protein and creatinine concentrations using a colorimetric enzyme assay (Labtest, Brazil). Creatinine clearance was calculated, to estimate the glomerular filtration rate, using the formula [(Urine (creatinine) × Urine Volume)/Serum (creatinine)].

Histology

The left kidney was excised, fixed with 4% buffered formaldehyde, embedded in paraffin and sectioned. The sequential 5 μm sections obtained were stained with hematoxylin-eosin and picrosirius. Hematoxylin-eosin staining allowed the investigation of glomerular morphological changes and picrosirius staining allowed collagen fibers detection. For the morphological investigation, each animal had 30 glomeruli analyzed, randomly. Bowman's capsule area, Bowman's space area, glomerular tuft area and glomerular tuft diameter were traced and calculated.

Renal cryosections (8 μm thick) were stained with Oil Red O and counterstained with hematoxylin to visualize accumulated lipid droplets. Collagen volume fraction and lipids volume fraction were determined by measuring the area of stained tissue within a given field and expressing that area as a proportion of the total area under observation. Digital images were taken of stained sections using a Leica microscope (Leica DM 1000) and every analysis were performed using the image analysis software Image Pro-Plus 4.1 (Media Cybernetics, Silver Spring, MD, USA).

Immunohistochemistry

Sections from the left kidney (4 μm) were incubated with the antibodies anti-fibronectin (Abcam, ab45688) and anti-Collagen type IV (Abcam, ab6586). After incubation, the sections were counterstained with hematoxylin. Immunostaining proportion was determined by measuring the area of immunostained tissue within a given field. Digital images were taken of stained sections using a Leica microscope (Leica DM 1000) and every analysis were performed using the image analysis software Image Pro-Plus 4.1 (Media Cybernetics, Silver Spring, MD, USA). The results were expressed as percentage of staining area.

Table 1. Metabolic parameters of SHR fed control diet and SHR fed high-fat diet after 8 weeks of protocol

Parameters	CD	HFD
Initial body weight (g)	44.8 ± 1.8	45.7 ± 1.2
Final body weight (g)	236 ± 4	230 ± 5
Retroperitoneal Fat (g)	0.76 ± 0.04	1.44 ± 0.09*
Periepididymal Fat (g)	0.54 ± 0.03	0.98 ± 0.03*
Glycemia (mg/dL)	102 ± 2	102 ± 3
AUC (mg/dl/min)	149 ± 4	185 ± 7*
Food intake (g/24 h)	22.6 ± 0.6	16.5 ± 0.6*
Calories intake (Kcal/24 h)	58 ± 1.6	62.9 ± 2.4

Data are expressed as mean ± SEM. CD = Control diet (n = 8), HFD = High-fat diet (n = 8). AUC = area under curve. Student's t test. *P ≤ 0.05 vs. CD.

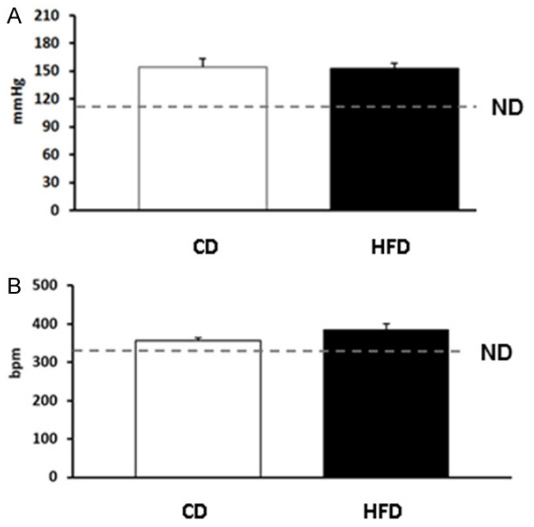

Figure 1. Mean arterial pressure (A) and heart rate (B) Error bars indicate the SEM. CD = control diet group (n = 6); HFD = high-fat diet group (n = 6); ND = normotensive Wistar group fed standard control diet during 8 weeks since post-weaning.

Statistical analysis

The results were analyzed by Student's t test and presented as mean ± standard error of the mean (SEM). A *p* value equal to or less than 0.05 was considered to be statistically significant. Statistical analysis was performed using the GraphPad Prism 6 software.

Results

Metabolic and cardiovascular parameters

There was no difference in the initial body weight as well as in the final body weight between the groups. However, high-fat diet induced a significant increase in the weight of periepididymal (88%) and retroperitoneal (89%) fat pads of HFD group compared with CD group. Despite the fasting glycemia was not different between groups, the consumption of HF diet since post-weaning induced glucose intolerance in SHR, evidenced by the increased area under the curve in the GTT of HFD group compared with CD group. The food intake was reduced in HFD group, but there was no difference in calories (kcal) intake during 24 h (**Table 1**). No differences in the mean arterial pressure and heart rate were observed between groups (**Figure 1**). In the **Figure 1**, control values showed by dashed lines were previously published by our group and can be used as reference of the normotensive animals submitted to the same experimental protocol [21].

Biochemical parameters

After 8 weeks of protocol, HFD group showed higher triglycerides level (194%), lower urinary volume (49%) and lower creatinine excretion (30%) than CD group (**Table 2**). There was no statistically significant difference between groups in the serum creatinine, serum cholesterol, and serum and urinary total proteins concentration. However, the consumption of a HF diet significantly reduced the glomerular filtration rate of HFD group by half when compared to the CD group (**Table 2**).

Renal morphological parameters

HF diet markedly increased renal lipid deposition in the HFD group (116%) compared with CD group (**Figure 2A** and **2B**). The high-fat diet also induced morphological damage in the renal glomerulus of the SHR, evidenced by optical microscopy (**Figure 3A**). There was a decrease in the glomerular tuft diameter (HFD: 82 ± 1 vs. CD: 88 ± 2 μm) and a reduction of the glomerular tuft area (HFD: 4733 ± 65 vs. CD: 5289 ± 171 μm^2) (**Figure 3B** and **3C**). Along with these responses, we observed an increase in Bowman's space area (HFD: 2194 ± 93 vs. CD: 1694 ± 42 μm^2) with no changes in the Bowman's capsule area (**Figure 3D** and **3E**).

The HF diet consumption also led to a higher renal fibrillar collagen deposition in the HFD group (62%) compared with the CD group (**Figure 4A**). Strikingly, SHR fed a HF diet had a two-fold increase in type IV renal collagen (8.2

Table 2. Biochemical parameters of SHR fed control diet and SHR fed high-fat diet after 8 weeks of protocol

Parameters	CD	HFD
Serum Triglycerides (mg/dL)	32.7 ± 2.4	96.2 ± 6.8*
Serum Creatinine (mg/dL)	0.5 ± 0.0	1,7 ± 0.8
Serum Total Proteins (mg/dL)	5.3 ± 0.3	5.1 ± 0.2
Serum cholesterol (mg/dL)	43.5 ± 3.3	46.5 ± 4.2
Urinary volume (mL/24 h)	11.9 ± 1.2	6.1 ± 1.3*
Urine Creatinine (mg/24 h)	1078 ± 46	754 ± 36*
Urine Total Proteins (mg/24 h)	4.4 ± 0.5	3.4 ± 0.3
Glomerular filtration rate (mL/min)	1.4 ± 0.1	0.7 ± 0.1*

Data are expressed as mean ± SEM. CD = control diet fed rats (n = 6) and HFD = High-fat diet fed rats (n = 6). Student's t test, *P ≤ 0.05 vs. CD.

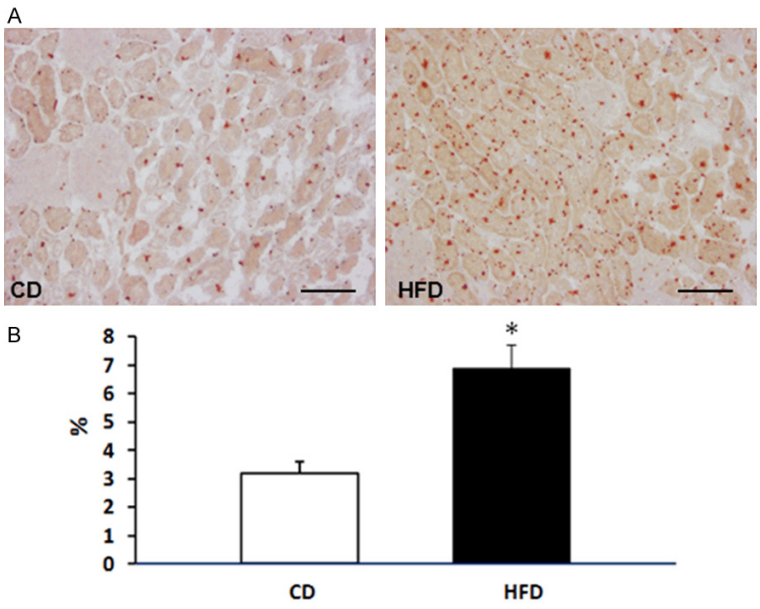

Figure 2. Renal lipids deposition. A. Representative images of renal tissue of spontaneously hypertensive rat (SHR) stained with Oil Red O. Magnification × 200. Bar = 100 μm. B. Quantification of renal lipids deposition. Error bars indicate the SEM. CD = control diet (n = 6); HFD = high-fat diet (n = 7). *P < 0.05 versus CD.

± 0.9 vs. 4.1 ± 0.7%) (**Figure 4B**). Parallel to the increased expression of type IV collagen, the renal expression of fibronectin was also increased in the HFD group compared to CD group (1.7 ± 0.2 vs. 0.9 ± 0.1%) (**Figure 4C**).

Discussion

In the present study, we demonstrated that SHR fed a HF diet since post-weaning develop in adulthood an increase in visceral adiposity, high serum triglycerides and glucose intolerance. We also demonstrated that the consumption of a HF diet since post-weaning induced an impairment in the renal function associated with significant structural alterations, such as higher lipid deposition, fibrillar collagen accumulation, increased type IV collagen and fibronectin expression, and lower glomerular tuft area compared with SHR fed a normal diet.

Previous study from our group demonstrated that the consumption of HF diet for 8 weeks, increased mean arterial pressure in Wistar rats [21]. In the present study, the mean blood pressure of SHR was unaltered by the diet. Thus, the consumption of a HF diet since post-weaning was not able to aggravate the ongoing hypertension in the HFD group. Similarly, the blood pressure of SHR fed a HF diet for 10 weeks was also unaltered in a study realized by Knight and colleagues [24]. However, SHR fed a HF diet for 15 weeks showed increased blood pressure [10, 25], suggesting that the effect of a HF diet in the arterial pressure of SHR could be time dependent. Furthermore, all studies involving SHR fed a HF diet that showed an increase in the mean arterial pressure started the protocol with adult or young adult rats [10, 25, 26]. The current literature shows that aging is strongly associated with increased cardiovascular impairments [27, 28]. Consequently, one should consider that the result of these studies had on the top of HF diet the influence of senescence.

In addition, HFD group showed no significant difference in the final body weight when compared with CD group. This response could be explained by the fact that SHR strain has a resistance to gain body weight during the development of obesity [29-32]. Despite the final body weight, SHR submitted to the consumption of the HF diet showed significant higher retroperitoneal and periepididymal fat pads

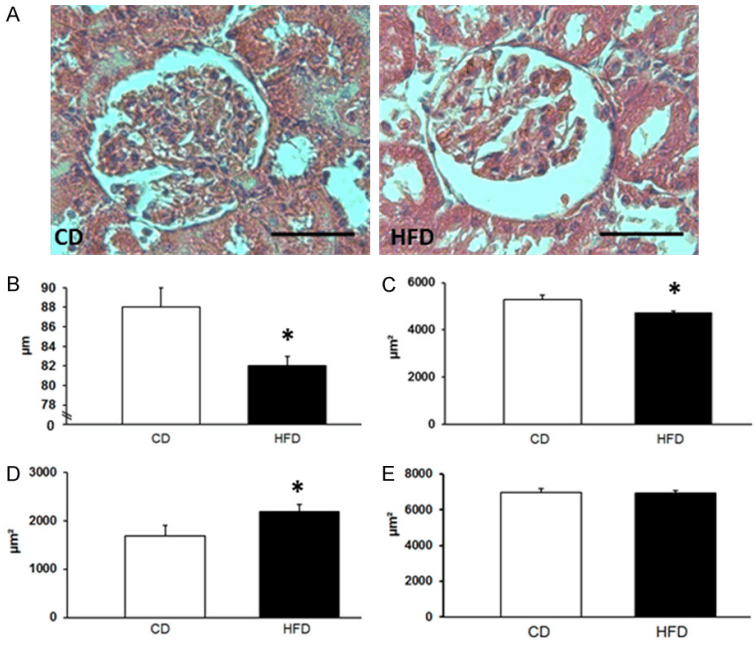

Figure 3. Glomerular morphology. A. Representative images of renal glomeruli of spontaneously hypertensive rat (SHR) stained with hematoxylin-eosin. Magnification × 400. Bar = 50 μm. SHR fed control diet (CD group). SHR fed high-fat diet (HFD group). B. Glomerular tuft diameter. C. Glomerular tuft area. D. Bowman's space area. E. Bowman's capsule area. Error bars indicate the SEM. CD = control diet (n = 6); HFD = high-fat diet (n = 6). *P < 0.05 versus CD.

than SHR fed control diet. Retroperitoneal and periepididymal fat pads are components of the visceral white adipose tissue [33], which is the form of obesity that is most strongly associated with the metabolic syndrome [34] and renal damage [35].

Visceral obesity can be linked with the development of renal injury through increased circulating triglycerides and free fatty acids. The adipose tissue is the major regulator of systemic lipid storage. However, when adipose tissue cannot expand further to store the excessive lipids, they accumulate in non-adipose tissues as ectopic fat [14, 36]. In this study, we observed significant higher lipid accumulation in the kidney of animals fed a HF diet when compared to CD group. Thus, this increase in renal lipid depots may be a potential mechanism to explain extracellular matrix accumulation and accelerated decline in renal function of SHR fed a HF diet since post-weaning.

The excessive renal deposition of extracellular matrix consists in a process called renal fibrosis and it is an important marker of the progression of CKD [37]. During adulthood, the SHR strain slowly develops renal fibrosis [38-40] and in the present study, we showed that the consumption of a HF diet since early period of life, accelerated the accumulation of extracellular matrix in the kidney of SHR, demonstrated by the significant higher fibronectin, collagen type IV and fibrillar collagen in the kidney of HFD group compared with CD group.

The deposition of lipid droplets into non-adipose tissues, such as the kidney, can lead to an accumulation of toxic metabolites followed by macrophage recruitment and an increase in fibrogenic cytokines, such as IL-1β, IL-6, TNFα [14, 41]. Transforming growth factor beta (TGF-β) is also an important fibrogenic factor that is increased in lipotoxicity [42]. TGF-β directly stimulates the synthesis of extracellular matrix components and blocks the degradation of extracellular molecules. This imbalance causes an excessive accumulation of fibronectin and different types of collagens [43], such as the changes presented herein in the kidney of SHR fed a HF diet since post-weaning.

In a study from Gu and Herrera [44], renal fibrosis was associated with a retraction of glomeruli capillary tufts in hypertensive patients. In the present study, we showed that besides the increase of extracellular matrix, hypertensive rats fed a HF diet had decreased glomerular tufts area and diameter than hypertensive rats fed a normocaloric diet, suggesting a glomeruli capillary tuft retraction. A possible reason for the tuft retraction can be due to an increased contractile tone of the mesangial cells in response to cytokines, such as IL-1 and TGF-β [45]. The capillary surface of glomerulus may change by the contraction of those cells, promoting alterations in the glomerular filtration rate [46]. Thus, the mesangial cells contraction could be a possible mechanism that connects the glomerular capillary tuft retraction with the

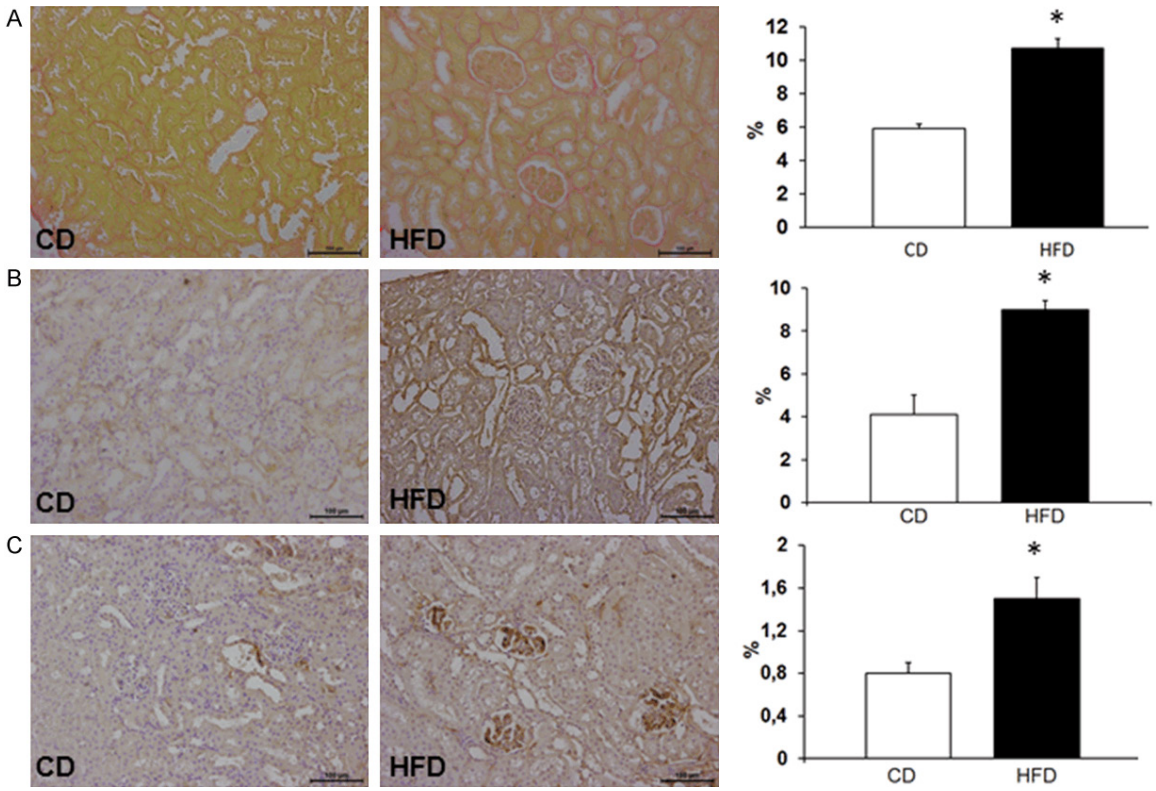

Figure 4. Renal quantification of collagen and fibronectin. A. Representative images of renal tissue of spontaneously hypertensive rat (SHR) stained with picrosirius and quantification of renal fibrillar collagen deposition. Magnification × 200. Bar = 100 µm. B. Representative images of renal tissue of spontaneously hypertensive rat (SHR) immunostained for collagen type IV and quantification of renal collagen type IV. Magnification × 200. Bar = 100 µm. C. Representative images of renal tissue of spontaneously hypertensive rat (SHR) immunostained for fibronectin and quantification of renal fibronectin. Magnification × 200. Bar = 100 µm. Error bars indicate the SEM. CD = control diet (n = 7); HFD = high-fat diet (n = 7). *P < 0.05 versus CD.

lower glomerular filtration rate observed in the HFD group when compared with CD group.

Conclusion

In conclusion, our data suggests that HF diet consumption since early period of life, increased adiposity, serum triglycerides and glucose intolerance. Furthermore, HF diet worsened renal damage in adult SHR, which can be associated with increased renal lipid accumulation. Taken together, our study reinforces the importance of interventions targeting reductions in HF intake from an early age, to prevent the metabolic and renal damage in individuals predisposed to hypertension later in life.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Vera Farah, Health and Biological Science Center of Mackenzie Presbyterian University, Rua da Consolacao, 930, Sao Paulo 01302-907, SP, Brazil. Tel: (55) (11) 2114 8159; E-mail: vera.farah@mackenzie.br

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