Contribution of increased expression of stearoyl-CoA desaturase-1 in adipose tissue to serum content of monounsaturated fatty acids in patients with chronic kidney disease

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Introduction Chronic kidney disease (CKD) is associated with a great cardiovascular burden. The risk of cardiovascular complications, including death, is several-fold higher in patients with CKD as compared with age-adjusted general population. Among major culprits responsible for this are lipid disturbances,[1] which increase cardiovascular risk both in the general population and patients with CKD by contributing to atherogenesis. Dyslipidemia is a constant feature of CKD.[2] Apart from the well-researched hypertriglyceridemia and low high-density lipoprotein cholesterol, it consists of severe disorders of fatty acid profile. We have previously shown that the content of serum monounsaturated fatty acids (MUFAs) is increased in patients with CKD and it might predispose them to cardiovascular risk.[3] The increase in MUFA content was observed despite similar diet when compared with controls, pointing to a hypothesis that it might derive from increased endogenous synthesis. The rate-limiting step in the formation of MUFA is the introduction of a double bond in the Δ9 position of acyl--CoA, catalyzed by an enzyme called stearoyl--CoA desaturase-1 (SCD1). Therefore, SCD1 activity is a determinant of the rate of the whole process of MUFA synthesis. Some authors suggest that increased endogenous MUFA synthesis by SCD1 is associated with metabolic diseases, and increased SCD1 activity has been proposed as a marker of cardiovascular disease (CVD) risk.[4] The expression of SCD1 is, in turn, controlled by a specific transcription factor, namely sterol regulatory element-binding protein 1c (SREBP-1c).

The aim of the present study was to clarify whether the activity of SCD1 in adipose tissue contributes to the increased content of serum MUFA in patients with CKD. Moreover, gene expression of SREBP-1c in adipose tissue was assessed to get further insight into the mechanisms responsible for the observed alterations in serum MUFA profile in those patients.

Methods Plasma samples were collected from 46 patients with CKD stage 5 (predialysis and dialyzed), as well as from 57 controls without CKD. Subcutaneous adipose tissue was taken from 22 of the patients with CKD at the time of kidney transplantation, and from 11 controls during hernia surgery. Serum and adipose tissue MUFA contents were assessed by gas chromatography–mass spectrometry as described previously.[3] SCD1 activity was estimated based on an oleic acid / stearic acid desaturation index (18:1/18:0 DI). SCD1 and SREBP-1c mRNA levels were measured in samples of subcutaneous adipose tissue of patients and controls by real-time reverse transcriptase–polymerase chain reaction. Dietary habits were assessed with the use of the Food Frequency Questionnaire with 6 answers (FFQ6).[5] FFQ6 is the most common dietary assessment tool used in epidemiologic studies, validated for Polish population. It consists of a list of 55 categories, further divided into specific foods or beverages. The major PUFA-rich products assessed included: oils, nuts, seeds, and various fish. The data are presented as mean and SD or median and interquartile range (IQR), as appropriate. The assumption

of normality was verified with the Kolmogorov–Smirnov test. A *P* value of less than 0.05 was considered significant. Comparisons between 2 groups were assessed with the *t* test or Mann–Whitney test, as appropriate. Correlations among the variables were evaluated with the Pearson correlation coefficient. Statistical processing of the results was performed with the statistical software STATISTICA PL version 13.3 (Statsoft, Kraków, Poland). The protocol of this study was approved by the local bioethics committee at the Medical University of Gdansk (protocol no. NKEBN/614/2013–2014) and informed consent was obtained from all participants.

Results Patients with CKD and controls were similar in age and sex. Similarly, there were no intergroup differences in the prevalence of obesity, type 2 diabetes, and metabolic syndrome. The major differences in lipid profile included higher triglyceride concentration (mean [SD], 197.4 [21.3] mg/dl vs 138.8 [12.6] mg/dl; *P* <0.01) and decreased high-density lipoprotein cholesterol level (mean [SD], 39.1 [3.9] mg/dl vs 53.8 [2.9] mg/dl; *P* <0.01) in patients with CKD as compared with controls. Concentrations of total and low-density lipoprotein cholesterol did not differ. MUFA content was increased in plasma (mean [SD], 32.6% [4.1] vs 29.1% [3.6]; *P* <0.01) and in adipose tissue (mean [SD], 58.2% [2.8] vs 55.9% [2.1]; *P* = 0.02) of patients with CKD as compared with controls. There was no difference in consumption of MUFA-rich foods between patients with CKD and controls. The 18:1/18:0 DI was also higher in patients with CKD, both in serum (mean [SD], 4.36 [0.89] vs 3.76 [0.75]; *P* <0.01) and in adipose tissue (mean [SD], 14.58 [4.29] vs 10.84 [1.60]; *P* = 0.02) (**FIGURE 1A**). The SCD1 mRNA was almost twice as high in the adipose tissue of patients with CKD when compared with controls (median [IQR], 3.84 [2.07–7.06] vs 2.27 [0.98–3.22]; *P* = 0.04) (**FIGURE 1B**). Similarly, the adipose tissue expression of SREBP-1c was increased in patients with CKD in comparison with controls (median [IQR], 0.104 [0.089–0.194] vs 0.052 [0.030–0.096]; *P* = 0.03) (**FIGURE 1C**). In adipose tissue, a positive association was observed between 18:1/18:0 DI and SCD1 mRNA (*r* = 0.43; *P* = 0.013), and between 18:1/18:0 DI and MUFA content (*r* = 0.70; *P* <0.01). Similarly, SCD1 and SREBP-1c gene expressions were tightly correlated (*r* = 0.63; *P* <0.01). There was an association in the tissue MUFA content and the serum MUFA (*r* = 0.47; *P* <0.01). In contrast, the correlation of 18:1/18:0 DI between the adipose tissue and serum was weak and insignificant (*r* = 0.27; *P* = 0.13).

Discussion In our previous study,[3] we have documented a steady increase in serum MUFA content at successive stages of CKD as well as associations between serum MUFA and markers of CVD. In fact, MUFA was proved to be a strong independent risk factor for CVD. The results of the present study confirmed previous observations about elevated MUFA content and elucidated potential mechanisms for the observed phenomena. We demonstrated that endogenous MUFA synthesis in adipose tissue may contribute to increased serum MUFA content in CKD.

Diet constitutes one of the major sources of plasma MUFA content, and differences in MUFA intake might impact endogenous MUFA levels.[6] However, in the present evaluation, the intake of foods rich in MUFA did not differ between the groups, as assessed by the FFQ6 diet questionnaire. In contrast, the activity of SCD1, the rate-limiting enzyme in MUFA synthesis that was evaluated based on the 18:1/18:0 DI, was increased in adipose tissue of patients with CKD as compared with controls. The idea that increased MUFA synthesis is a major cause for elevated MUFA content was supported by a considerable increase in the gene expression of SCD1. Furthermore, gene expression of SREBP-1c in adipose tissue was also increased in patients with CKD. This transcription factor determines the expression and activity of SCD1. Mice expressing SREBP-1c have increased expression of SCD1 and increased synthesis of MUFAs, while knockout of SREBP-1c decreases SCD1 expression.[7,8] Increased SREBP-1c expression in adipose tissue of patients with CKD was consistent with previous studies from our center, in which a marked increase in both precursor and mature form of SREBP-1 has been found in white adipose tissue of rats with experimentally induced CKD.[9]

The exact mechanism through which endogenously increased MUFA levels impact the cardiovascular risk remains unclear. Taking into account that MUFAs are, most probably, the main substrates for the synthesis of hepatic triglycerides, it is plausible that the observed increase in their synthesis contributes to hypertriglyceridemia, a constant complication of advanced CKD. Hypertriglyceridemia increases the risk of CVD in the general population.[10] It is also acknowledged by some authors as a risk factor for CVD in patients with CKD.[11]

There are also reports linking increased SCD1, endogenous MUFA, and chronic inflammatory state, which predisposes both patients with CKD and the general population to cardiovascular risk.[12]

The limitation of the study that needs to be addressed is that the highest activity of SCD1 is observed in liver and in visceral adipose tissue. Therefore, these tissues would have been optimal for evaluating the contribution of SCD1 activity to elevated MUFA content. This is probably the reason for the observed lack of correlation of 18:1/18:0 DI between the adipose tissue and serum samples. However, liver and visceral adipose tissue were inaccessible for obvious ethical reasons.

To conclude, our results suggest that increased serum MUFA in patients with CKD, a potential contributor to increased cardiovascular risk,

FIGURE 1 Comparison of adipose tissue between patients with chronic kidney disease (CKD) and controls: **A** – oleic acid / stearic acid desaturation index (18:1/18:0 DI); $P = 0.02$; **B** – gene expression of stearoyl-CoA desaturase-1 (SCD1); $P = 0.04$; **C** – gene expression of sterol regulatory element-binding protein 1c (SREBP-1c); $P = 0.03$
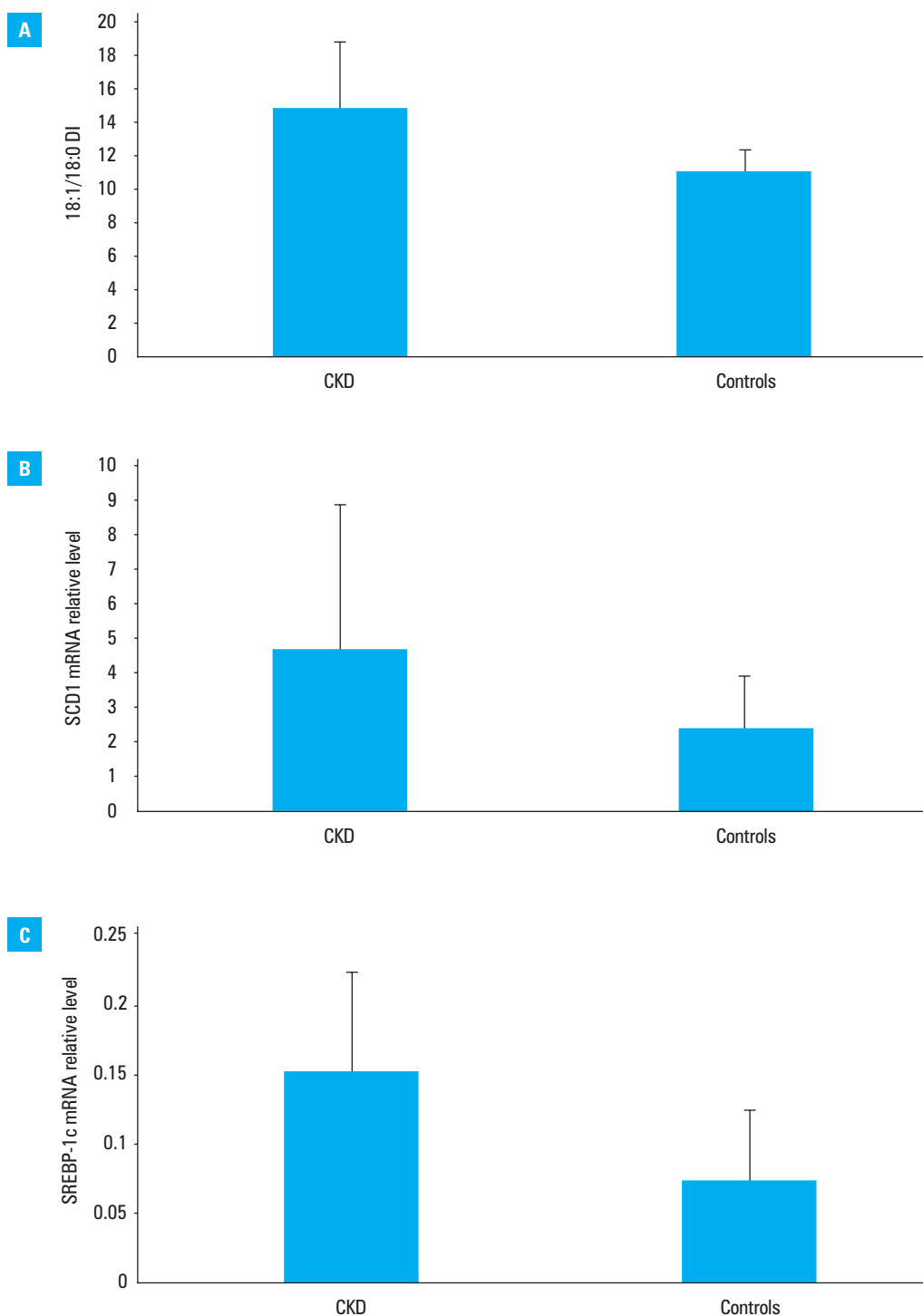
results mainly from increased endogenous synthesis by SCD1, driven by SCD1 transcription factor, SREBP-1c. Although liver as well as visceral adipose tissue depots are probably the main sites of increased endogenous MUFA synthesis, subcutaneous adipose tissue might also significantly contribute to this process.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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