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Increased expression of stearoyl-CoA desaturase (SCD1) in the adipose tissue contributes to serum content of monounsaturated fatty acids (MUFA) in patients with chronic kidney disease

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**Short title:** SCD1 in the adipose tissue contributes to serum MUFA in CKD

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**Introduction:** Chronic kidney disease (CKD) is a state characterized by enormous cardio-vascular burden. The risk of cardio-vascular complications, including death, is several times higher in CKD patients, as compared to age adjusted general population. Lipid disturbances are among the major culprits for the above phenomenon [1]. Contributing to atherogenesis, they increase cardio-vascular risk both in the general population, and in CKD patients. Dyslipidaemia is a constant feature of CKD [2]. Apart from the well acknowledged hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol, it consists of profound disorders of fatty acids (FA) profile. We have previously shown that the content of serum monounsaturated fatty acids (MUFA) is increased in CKD, and might predispose the patients to cardio-vascular risk [3]. The increase in MUFA content was observed despite similar diet when compared to 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 Δ-9 position of acyl-CoA, catalyzed by an enzyme called stearoyl-CoA desaturase (SCD1). Therefore, SCD1 activity is acknowledged as 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 cardio-vascular disease (CVD) risk [4]. The expression of SCD1 is, in turn, controlled by a specific transcription factor, named sterol regulatory element – binding protein (SREBP-1c). The aim of the present study was to clarify if the activity of SCD1 in adipose tissue contributes to the increased content of serum MUFA in CKD patients. 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 the course of CKD.

**Methods:** Plasma was collected from 46 patients with CKD stage 5 (pre-dialysis and dialyzed), as well as from 57 controls without CKD. Subcutaneous adipose tissue was taken
from 22 of the abovementioned CKD subjects at the time of kidney transplantation, and from 11 controls during hernia surgeries. Serum and adipose tissue MUFA content were analysed by gas chromatography - mass spectrometry as described previously [3]. SCD1 activity was estimated based on an oleic acid (18:1)/stearic acid (18:0) desaturation index (DI). SCD1 and SREBP-1c mRNA levels were measured in the subcutaneous adipose tissues of patients and controls by RT-RealTime PCR. Dietary habits were assessed with the use of an FFQ6 (Food Frequency Questionnaire) [5]. FFQ6 is the most common dietary assessment tool used in epidemiologic studies, validated for Polish population. It consists of a list of 55 line items, where each line item is defined by a series of foods or beverages. The major PUFA-rich products assessed included: oils, nuts, seeds, and various fish. The data is presented as means and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The assumption of normality was verified with the Kolmogorov-Smirnov test. A p-value < 0.05 was considered to be statistically significant. Comparisons between two groups were assessed with a Student’s t-test, or a Mann-Whitney test, as appropriate. Correlations among the evaluated variables were evaluated with Pearson’s correlation coefficient (r). Statistical processing of the results was performed with the use of the statistical software STATISTICA PL v 13.3 (Statsoft, Krakow, 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 the patients.

**Results:** The CKD patients and controls were similar in terms of age and gender. 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 in CKD (197.4 (21.3) vs. 138.8 (12.6) mg/dl; p<0.01), and decreased HDL cholesterol level (39.1 (3.9) vs. 53.8 (2.9) mg/dl; p<0.01), as compared to controls. Concentrations of total and low-density lipoprotein (LDL) cholesterol did not differ
significantly. MUFA content was increased in plasma of CKD patients (32.6 (4.1) % vs. 29.1 (3.6) %; p < 0.01), and in the adipose tissue (58.2 (2.8) % vs. 55.9 (2.1) %; p = 0.02), as compared to controls. There was no significant difference in consumption of MUFA rich foods between CKD patients and control subjects. The 18:1/18:0 desaturation index was also significantly higher in CKD, both in serum (4.36 (0.89) vs. 3.76 (0.75); p < 0.01) and in the adipose tissue (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 CKD patients, when compared to controls (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 significantly increased in CKD subjects in comparison to controls (0.104 (0.089-0.194) vs. 0.052 (0.030-0.096); p=0.03) (Figure 1C). In the adipose tissue, a positive significant 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 a significant 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, 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 cardio-vascular disease [3]. In fact, MUFA turned out as a strong independent risk factor for cardio-vascular disease. The present study confirms the previous observations of elevated MUFA content, and elucidates the potential mechanisms for the observed phenomena. It demonstrates that endogenous MUFA synthesis in the adipose tissue may contribute to increased serum MUFA content in the course of 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, evaluated through the 18:1/18:0 desaturation index, was significantly increased in the adipose tissue of CKD subjects, as compared to controls. The concept of increased MUFA synthesis, as the major cause for elevated MUFA content, was supported by the finding of a considerable increase in the gene expression of SCD1. Furthermore, gene expression of SREBP-1c in the adipose tissue was also increased in CKD patients. 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]. The finding of increased SREBP-1c expression in the adipose tissue of CKD patients stays in accordance 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 impact the cardiovascular risk remains unclear. Taking into account that they are, most probably, the main substrates for the synthesis of hepatic triglycerides, it is plausible that the observed increase in MUFA 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 CKD patients [11].

There are also reports linking increased SCD1, endogenous MUFA, and chronic inflammatory state that predisposes to cardio-vascular risk, both in CKD and in the general population [12]. The limitation of the study that needs to be addressed is that the highest activity of SCD1 is present in liver and in the visceral adipose tissue. Therefore, these tissues would have been
optimal for evaluating the contribution of SCD1 activity to elevated MUFA content. Probably, this the reason for the observed lack of correlation of 18:1/18:0 DI between the adipose tissue and serum. However, the liver and visceral adipose tissue have been inaccessible for obvious ethical reasons.

To conclude, our results suggest that increased serum MUFA in CKD patients, a potential contributor to increased cardio-vascular risk, 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.

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References:


Figure 1. (A) The 18:1/18:0 desaturation index, \( p = 0.02 \); (B) gene expression of stearoyl-CoA desaturase (SCD1), \( p = 0.04 \); (C) gene expression of sterol regulatory element – binding
protein 1c (SREBP-1c), p = 0.03, in the adipose tissue of chronic kidney disease (CKD) patients and controls.