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BRIEF REPORT

Insulin-like growth factor 1 and dehydroepiandrosterone levels in alcoholic liver cirrhosis

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Introduction

Sarcopenia is a common phenomenon in liver cirrhosis (LC), where it is closely correlated to morbidity and mortality.[1,2] Suspected reason for sarcopenia in LC is a lack of anabolic hormones, but this has only been demonstrated for insulin-like growth factor 1 (IGF-1) and for testosterone in male patients.[3,4]

In this study, we prospectively measured the levels of two anabolic hormones in a mixed group of male and female cirrhotic patients: IGF-1 as an example of an anabolic peptide, and dehydroepiandrosterone (DHEA) as an example for a steroid that is present in both sexes. We then correlated the results to the Child–Pugh scores of our patients and to a group

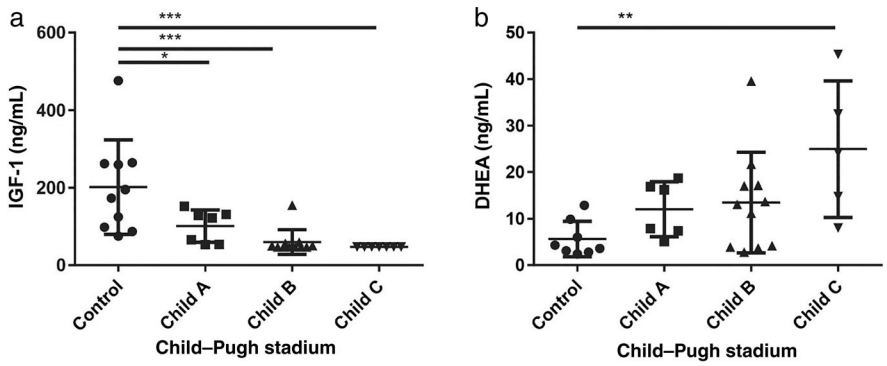

Figure 1 Comparison of insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone (DHEA) levels in patients with liver cirrhosis depending on their Child–Pugh score. Single values are given as concentration ng/mL, whereas short lines depict mean values ± SD. ANOVA and Tukey post hoc tests following symbol pinpoints show significant differences: $*P = 0.05$, $P = 0.01$, and $P = 0.001$.

of healthy controls, the hypothesis being both would be lower in the LC group and within this group even lower with higher scores.

Methods

Blood samples were drawn from 22 patients with LC. All were alcohol-induced and, at the time of being included, abstinent. Nine were female, 13 were male, mean age was 64 ± 14 years. We additionally drew samples from 8 healthy controls. One was female, 7 were male, mean age was 63 ± 10 years. DHEA and IGF-1 levels were measured using commercial ELISA kits (Test kit 1: EQ6154-9601, Euroimmun AG, Luebeck, Germany. Test kit 2: AB108873, Abcam PLC, Cambridge, UK). Test kit 1 is highly specific for DHEA, with cross-reactivity for DHEA-S or 16 hydroxydehydroepiandrosterone sulfate (16-OH-DHEA) below 0.05%. Detection limit of test kit 2 was 42.7 ng/mL IGF-1.

Sarcopenia was assessed in all patients and controls using the SARC-F questionnaire (Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls). All individuals with SARC-values ≥4 were counted as sarcopenic.[5,6] Additionally, all individuals underwent a handgrip strength test. Here, values ≤18 kg for women or 25.5 kg for men were counted as sarcopenic.[7]

For LC patients, Child–Pugh Scores were calculated out of existing clinical data.

All procedures followed were in accordance with the standards of the responsible committee on human experimentation (Study No. SAKL E-01-20 190 412) and the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients included in the study.

Results

Mean IGF-1 level in the control group was 202 ± 115 ng/mL (Fig. 1a). Mean IGF-1 levels in the LC group were significantly lower compared to controls at 101 ± 39 for Child A patients ($P = 0.03$), and 75 ± 40 for Child B patients ($P < 0.001$). Levels in all Child C patients were below the detection limit of 42.7 ng/mL ($P < 0.001$). Mean DHEA level in the control group was 5.6 ± 3.8 ng/mL (Fig. 1b). Mean DHEA levels in the LC group were 12 ± 5.9 ng/mL ($P = 0.6$) for Child A patients, 13.5 ± 10.8 ng/mL ($P = 0.3$) for Child B patients, and 25 ± 14.7 ng/mL ($P = 0.006$) for Child C patients.

Sarcopenia, as defined by SARC-values ≥4, was present in 1 out of 8 controls (12.5%), 1 out of 6 Child A patients (16.67%), 6 out of 11 Child B patients (54.54%), and 4 out of 5 Child C patients (80%). Sarcopenia, as defined by Handgrip strength values ≤18 kg for women or 25.5 kg for men, was present in 1 out of 8 controls (12.5%), 2 out of 6 Child A patients (33.3%), 7 out of 11 Child B patients (72.75%), and 4 out of 5 Child C patients (80%) (Table 1).

In sarcopenic individuals of any definition, the median IGF-1 level was 48.7 ng/mL (min 47.2; max 476.2), median DHEA level was 12.1 ng/mL (min 2.8; max 45.3). In non-sarcopenic individuals, median IGF-1 level was 104.7 ng/mL (min 47.2; max 195.4), median DHEA level was 8.9 ng/mL (min 2.4; max 24.2) (Fig. 2).

Discussion

It is generally suspected that sarcopenia in liver cirrhosis is due to decreased levels of various anabolic hormones.[4,9] In this study, we tested that hypothesis on two exemplary hormones: IGF-1 was chosen as a peptide that is unrelated to sex hormones. DHEA was chosen as a steroid that is not only a progenitor of male and female sex hormones alike, but that also acts as an anabolic hormone in

Table 1 Percentage of sarcopenic individuals in each group as determined by Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls (SARC-F) and handgrip strength test

	SARC-F (%)	Handgrip strength (%)
Control	12.5	12.5
Child A	16.67	33.33
Child B	54.54	72.72
Child C	80	80

Sarcopenia was diagnosed if SARC-F questionnaire returned a value ≥4, or if measured handgrip strength was below 25.5 kg for men or 19 kg for women respectively.[5,8] A trend of higher sarcopenia rates with higher Child–Pugh values is visible.

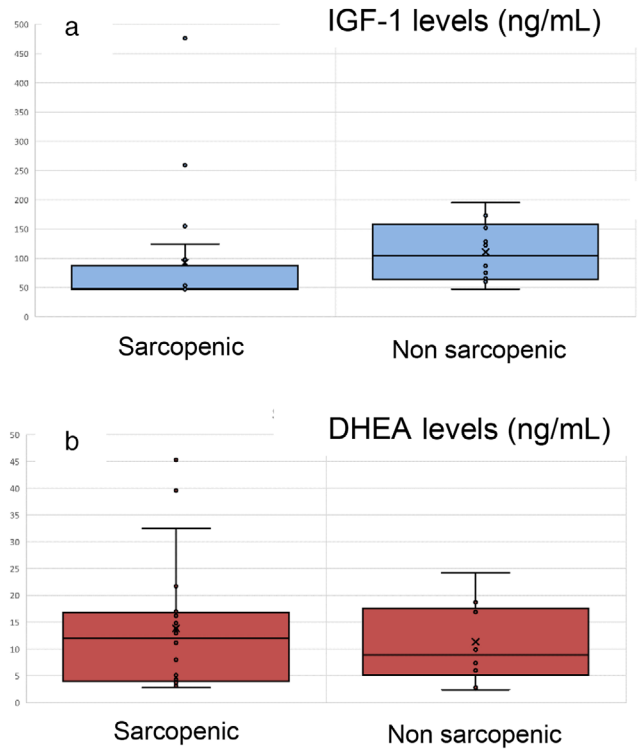

Figure 2 Insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone (DHEA) levels in sarcopenic and non-sarcopenic individuals. Because of the small sample size and skewed distribution, no inferential statistics procedures were performed.

both sexes itself by directly or indirectly enhancing protein synthesis, muscle growth, and muscle strength.[10,11]

Our results confirm that IGF-1 is indeed decreased in LC patients. In the case of DHEA, we expected this hormone to be decreased too, as it was demonstrated, for example, in hepatitis C fibrosis.[12] In contrast, levels of DHEA were surprisingly elevated in our patients compared to controls, and they increased with increasing Child–Pugh scores. To our knowledge, this is the first time such an increase in DHEA in LC is reported. However, DHEA metabolites like 16-OH-DHEA-S have been shown to be elevated in non-alcoholic liver fibrosis, so this result may be unexpected but not completely improbable.[13]

There was also a trend of lower IGF-1 levels and higher DHEA levels in sarcopenic individuals, but because of the small sample size, it was not tested for significance.

At the moment, we can only speculate about the reasons: One possibility would be an enzymatic block in the synthesis of sexual hormones. This would explain both the accumulation of DHEA as a metabolic intermediate and the lowered levels of testosterone found by other authors.[3,4,14] However, the conversion of DHEA mostly takes place not in the liver but in other tissues, so there is no obvious reason for a block here. An alternative explanation would be that in cirrhosis, DHEA is actively upregulated in an attempt to counteract sarcopenia.[15]

Both mechanisms are possible in principle, but none of them is proven. Additionally, none of them would explain the ineffectiveness of the raised DHEA levels in averting sarcopenia in liver cirrhosis.

To put it into perspective, this is a short report on a preliminary study, and as such, it has limitations. First, it is based on a small single cohort, so there is the possibility of pseudo-significance. Secondly, to keep the group consistent, we intentionally limited it to alcohol-induced LC. So theoretically, it is possible that a different cohort of non-alcoholic cirrhosis patients would show different results. Also for consistency, we limited it to two representative hormones and did not test for their metabolites. We have already started a more extensive prospective study that will hopefully clarify these points.

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