LPCN 1144 Resolves NAFLD in Hypogonadal Males

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Hypogonadism affects hepatic lipid metabolism and is expected to promote nonalcoholic fatty liver disease (NAFLD). The aims of this study were to determine (1) the prevalence of NAFLD in hypogonadal males and (2) the impact of correction of hypogonadism by LPCN 1144 (Lipocine, Inc., Salt Lake City, UT), an oral testosterone prodrug, on NAFLD in this population. Data were derived from a multicenter open-label single-arm trial of LPCN 1144 for hypogonadal males, in which a subset (n = 36) had serial magnetic resonance imaging–proton density fat fraction measurements (National Clinical Trial 03868059). NAFLD prevalence, defined by magnetic resonance imaging–proton density fat fraction ≥5%, was 66%. Eighty-one percent of those with baseline liver fat (BL) ≥5% had improvement in liver fat content, and NAFLD resolved in 33% of subjects at 8 weeks (mean relative reduction: 45%) and 48% (mean relative reduction: 55%) after 16 weeks of LPCN 1144 therapy. The reduction in liver fat was greater in those with higher BL (BL ≥5%: 71%; BL ≥8%: 80%; and BL ≥10%: 75%). Normalization rate of alanine aminotransferase and gamma-glutamyltransferase greater than the upper limit of normal range were 100% and 50% of treated patients, respectively. LPCN 1144 was not associated with major adverse events. *Conclusion:* Treatment with LPCN 1144 (oral T prodrug) in hypogonadal males with NAFLD resolved NAFLD in approximately half of the affected patients without any safety signals. Further studies are needed to validate its use in hypogonadal males with nonalcoholic steatohepatitis. (*Hepatology Communications* 2020;4:1430-1440).

The clinical and histological spectrum of nonalcoholic fatty liver disease (NAFLD) ranges from steatosis to nonalcoholic steatohepatitis (NASH) and fibrosis, and eventually to cirrhosis.[1] The prevalence of NAFLD is rising rapidly and is now recognized as a leading indication for liver transplantation worldwide.[2] NAFLD is linked with visceral fat accumulation and metabolic syndrome,[3,4] and is associated with increased risk of cardiovascular disease and mortality.[5] Obesity, type 2 diabetes, and dyslipidemia are the main metabolic risk factors for NAFLD.[6]

There are several lines of evidence suggesting a potential role of sex hormones in the genesis and

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline liver fat; BMI, body mass index; EOS, end of study; GGT, gamma-glutamyltransferase; IRB, institutional review board; LFS, liver fat study; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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progression of NAFLD. Sarkar et al. found that low testosterone was prevalent in patients with NAFLD with NASH fibrosis.[31] Both estrogen and androgen receptors are expressed in the liver.[7,8] Sex steroids influence hepatic metabolism and other biological pathways relevant for NASH.[9] These steroids further affect metabolic pathways in adipose tissue and other organs as well.[10,11] Studies suggest the presence of a link between obesity and low testosterone, as 33% of males with obesity have low levels of circulating testosterone even after correcting for age.[12,13] Testosterone has several biological functions that affect metabolic homeostasis. It keeps visceral adipose tissue volume down by promoting the commitment of pluripotent cells of mesenchymal origin into myogenic lineage *in vitro*, by inhibiting adipogenic differentiation.[14] By increasing and maintaining the muscle mass, testosterone enhances the capacity of muscles to oxidize free fatty acids (FFAs) in the fasted state, and can therefore decrease the amount of FFAs available for hepatic uptake in the interdigestive state.[15,16] Testosterone also improves insulin sensitivity, thereby enabling more efficient glucose disposal in the postprandial state and reducing hepatic carbohydrate delivery to the liver, where it may serve as a substrate for *de novo* lipogenesis.[17,18] These biological functions support the plausibility that hypogonadism in males, manifested by a low free testosterone level, may contribute to the development of NAFLD and prime the patient for disease progression.

Recently, a study investigating the effect of parenteral testosterone treatment on liver enzymes showed that restoring serum testosterone concentrations to normal levels improved the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as body mass index (BMI), waist size, and lipid profile.[19] LPCN 1144 (Lipocine, Inc., Salt Lake City, UT) is an oral prodrug of bioidentical testosterone that is absorbed through intestinal lymphatics and intended for the treatment of hypogonadism in males. LPCN 1144 was well tolerated with no severe cardiac or hepatic disorders (including cholestasis and hepatocellular carcinoma) in over 15 clinical studies with a total of 726 subjects up to 1 year (e.g., NCT02081300, NCT03868059, NCT04134091).

We hypothesized that there exists a relationship between hypogonadism in obese males and the presence of NAFLD, and that correction of hypogonadism would ameliorate NAFLD. We tested this hypothesis as part of a phase 2a clinical trial investigating the safety and efficacy of LPCN 1144 for the treatment of male hypogonadism. The specific aims were to (1) determine the prevalence of NAFLD within a population of hypogonadal males and the relationship of circulating testosterone levels with the presence and severity of NAFLD, (2) evaluate the impact of LPCN 1144 on hepatic steatosis and markers of liver injury in hypogonadal men, and (3) assess the safety and tolerability of LPCN 1144 in this population.

Patients and Methods

The LPCN 1144 liver fat study (LFS) was a 16-week, open-label, multicenter, single-arm study to assess the effect of LPCN 1144 on liver fat by a magnetic resonance imaging–proton density fat fraction (MRI-PDFF) technique in hypogonadal male subjects (n = 36). This was a subcohort within a larger study investigating the effects of LPCN 1144 on ambulatory blood pressure (n = 144) (NCT

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03868059). Institutional review board (IRB) approval of the protocol, informed consent, and subject information and/or advertising, as relevant, was obtained before the authorization of drug shipment to a study site. Any amendments to the protocol required IRB approval before implementation of any changes made to the study design. The investigator was required to submit, maintain, and archive study-essential documents according to the International Conference on Harmonization (ICH). Serious adverse events that met the reporting criteria, as dictated by local regulations, were reported to both IRB and regulatory agencies as required by local regulations. During the conduct of the study, the investigator promptly provided written reports (e.g., ICH expedited reports or any additional reports required by local regulations) to the IRB of any changes that affected the conduct of the study and/or increased the risk to subjects. Written documentation of the submission to the IRB was also provided to the sponsor/principal investigator. Informed consent in writing was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the IRB. All of the data were provided by the study sponsor to the investigators who worked with the sponsor, to generate the data tables and figures. The authors take responsibility for the contents of the manuscript.

PATIENT POPULATION

The inclusion criteria for the study were as follows: males 18-80 years of age with documented onset of hypogonadism before the age of 65 years, diagnosis of primary or secondary hypogonadism (congenital or acquired), and two consecutive-morning (6-10 AM) blood-sample concentrations of serum total testosterone less than 300 ng/dL on separate days. Those who had previously received androgen therapy were allowed to enroll after washout from androgen therapy. The washout duration depended on the type of previously administered androgen therapy. The washout following intramuscular androgen injections, topical or buccal androgens, and oral androgens were 12, 4, and 3 weeks, respectively.

The key exclusion criteria included a history of sensitivity or allergy to androgens or product excipients, clinically significant abnormal labs (hemoglobin <11.5 or >16.0 g/dL, hematocrit <35% or >54%, serum transaminases >2.5 × upper limit of normal, serum bilirubin >2.0 mg/dL, creatinine >2.0 mg/dL, prostate-specific antigen >4 ng/mL, and prolactin >17.7 ng/mL), abnormal breast examination, systolic blood pressure [BP] >160 mmHg or diastolic BP >100 mmHg, and moderate to severe benign prostatic hyperplasia. These criteria were developed primarily to address safety concerns related to the use of sex hormones or to reduce the possibility of confounding by additional disease processes that could be affected by sex hormones (high prolactin). Those with a history of alcohol consumption over the threshold levels of three units of alcohol daily within the previous year were excluded.

STUDY DESIGN

This study was a prospective, multicenter, single-arm, open-label study in which a substudy was performed to evaluate liver fat by MRI-PDFF (Supporting Fig. S1). The study involved six visits. Subjects were screened for hypogonadism at visits 1 and 2. At visit 3, baseline ambulatory blood pressure was monitored for 24 hours before initiating LPCN 1144 therapy. LPCN 1144 was distributed at visit 4 (day 1). An MRI-PDFF test was separately scheduled between visits 2 and 4, to assess baseline liver fat for subjects participating in the liver fat substudy. For subjects participating in this study, an interim visit was held at week 8 to measure liver fat by MRI-PDFF. At visit 5 (week 16), liver fat and ambulatory blood pressure monitoring were carried out, and the study drug was discontinued. Exit procedures were performed at visit 6.

The study intervention was the oral administration of LPCN 1144, an orally bioavailable prodrug of bioidentical endogenous testosterone, twice a day, 225 mg TU (450 mg TU daily), about 30 minutes after a meal.

All subjects were free to withdraw any time and were withdrawn if they met any of the following criteria:

- Any event, in the judgment of the investigator, in which continuation of the subject in the trial could put the subject at health risk;
- Significant noncompliance with the protocol requirements; and
- Lost to follow-up.

Blood samples for all subjects were obtained at visit 2 for baseline clinical lab tests, and at visit 6 before morning meals, before the exit process. Hematology, serum chemistry, and urinalysis tests were conducted by Medpace Central Laboratories (Cincinnati, OH). Laboratory reference ranges were obtained before the initiation of the study.

ENDPOINTS AND STATISTICAL ANALYSIS

The endpoint was to assess changes in hepatic fat content measured by MRI-PDFF from baseline to interim (~week 8) and following treatment (~week 16, end of study, EOS). Statistical analyses were performed with the full analysis set, consisting of all subjects eligible by MRI-PDFF at baseline, interim, and EOS. The PDFF value was derived with:

$$\text{PDFF}(\%) = \frac{M_f}{\left(M_w + M_f\right)} \times 100,$$

where PDFF (%) is the percentage of liver fat calculated by the equation; M_f is magnitude of the fat component signal; and M_w is magnitude of the water component signal. The measured liver fat percentage was obtained from an average of three regions of interest in the liver. The measured liver fat fractions were validated based on comparison with the reference values measured using the fat fraction phantom vials provided and certified by Calimetrix: a Bland-Altman analysis with 95% limit of agreement ($1.96 \times \sigma$) was performed between quantitative measure and reference values. The principal measures of liver injury were the circulating levels of AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT). Descriptive statistics were used to define the characteristics of the group at baseline. Absolute and relative changes in MRI-PDFF were computed, and the distribution of liver fat percentage was compared from baseline to EOS. Furthermore, the proportion of individuals with decrease in steatosis to less than 5% (i.e., NAFLD resolution), the threshold value for the diagnosis of NAFLD, was also determined. The correlation between changes in steatosis and body weight were also estimated. Changes in levels of liver enzymes reflective of liver injury (AST, ALT, and GGT) were also similarly analyzed. A P value of less than 0.05 was considered to be significant.

Results

This study (LFS) included a total of 36 hypogonadal males. They represent a subset of individuals who enrolled in a trial of LPCN 1144 to determine the effect of testosterone replacement therapy in hypogonadal males on ambulatory blood pressure. The baseline demographic features of the participants of the LFS were similar to those of the original study population (Table 1). Within this LFS population, 21 individuals had greater than or equal to 5% of hepatic steatosis and therefore met criteria for NAFLD. The disposition of patients through the study is shown in Supporting Fig. S1. Thirty-three individuals enrolled in this LFS completed 16 weeks of treatment, and 32 were eligible for the analyses: full analysis set.

NAFLD WAS HIGHLY PREVALENT IN HYPOGONADAL MALES

The distribution of liver fat scores at entry into the study is shown in Fig. 1A. Twenty-one of the 32 (66%) participants in this study had hepatic steatosis, defined as liver fat fraction ≥5%. The mean MRI-PDFF was 12.1% (SD ± 8.1). Eight individuals (25%) had a hepatic fat fraction of 10% or higher. Of note, the liver fat percentage were not normally distributed as shown in Fig. 1A. The hepatic fat content was also related to baseline BMI and ALT levels, with P = 0.02 (Supporting Fig. S2A,B and Table 2).

LPCN 1144 TREATMENT WAS ASSOCIATED WITH IMPROVEMENT IN HEPATIC FAT CONTENT

At the end of the study, 63% (20 of 32) of the study population had less than 5% liver fat as measured by MRI-PDFF, and 91% (29 of 32) had less than 10% fat fraction. NAFLD resolved in 33% of subjects at 8 weeks (mean relative reduction [RR]: 45%) and 48% (mean RR: 56%) after 16 weeks of LPCN 1144 therapy (Fig. 1B). The change in absolute liver fat content for the group ranged from

TABLE 1. BASELINE CHARACTERISTICS AND MORBIDITIES OF LFS POPULATION IN FULL ANALYSIS SET

		LPCN 1144
		Dose: 225 mg twice daily
Parameter	Statistics	n = 32
Age	Mean (SD)	50.4 (10.1)
Race		
American Indian or Alaska Native	n (%)	0
Asian	n (%)	0
Black or African American	n (%)	4 (12.5)
Native Hawaiian or other Pacific Islander	n (%)	0
White	n (%)	27 (84.4)
Other	n (%)	1 (3.1)
Ethnicity		
Hispanic or Latino	n (%)	13 (40.6)
Non-Hispanic or Latino	n (%)	19 (59.4)
Not reported	n (%)	0
Unknown	n (%)	0
BMI (kg/m^2)	Mean (SD)	33.8 (6.59)
Weight (kg)	Mean (SD)	104.3 (22.9)
Comorbidity		
Obesity	Mean (SD)	25 (78.1)
Type 2 diabetes mellitus	Mean (SD)	8 (25.0)
Hypertension	Mean (SD)	13 (40.6)
Baseline serum testosterone concentration (ng/dL)	Mean (SD)	202.5 (66.0)
Baseline MRI-PDFF (%)	Mean (SD)	8.86 (7.91)
Baseline hemoglobin A1c* (%)	Mean (SD)	6.09 (1.30)
Baseline total cholesterol (mg/dL)	Mean (SD)	191.8 (33.2)
Baseline HDL cholesterol (mg/dL)	Mean (SD)	39.9 (10.2)
Baseline LDL cholesterol (mg/dL)	Mean (SD)	119.5 (32.6)
Baseline triglycerides (mg/dL)	Mean (SD)	175.0 (90.8)

*Glycated hemoglobin: hemoglobin A1c.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

+2.1% to −16.4%. Although 12 of 32 individuals experienced a small increase or no change in hepatic fat content over the study duration, most (20 of 32, 63%) experienced a decrease in liver fat content. Among those who had NAFLD (≥5% steatosis) at baseline, 17 of 21 (81%) individuals experienced an improvement in hepatic fat content (Fig. 1C). Those with greater baseline liver fat had larger decreases with 16 weeks of LPCN 1144 treatment; the mean relative decrease in liver fat content was 33% in all individuals with NAFLD, whereas it was 40% in those with baseline hepatic MRI-PDFF greater than 10% (Fig. 1D).

LPCN 1144–MEDIATED DECREASE IN HEPATIC FAT FRACTION IS INDEPENDENT OF CHANGES IN BODY WEIGHT

The mean baseline weight and BMI of the participants were 104.3 (±22.9) kg and 33.8 (±6.6) kg/m^2, respectively. The degree of decrease in liver triglyceride content was linked to the severity of underlying obesity; those with a baseline BMI >40 kg/m^2 had the greatest decrease in liver fat (Fig. 2A). Twenty-six of 32 individuals experienced some weight gain or no changes in body weight during the study period (Fig. 2B1,B2). Thus, the observed decrease in liver fat content in 20 of 32 individuals noted previously was not attributable to weight loss. Similarly, when only those who had NAFLD (≥5% steatosis) at baseline were considered (Fig. 2C), 18 of 21 (86%) experienced weight gain or no change in weight during the study duration, further supporting the inference that the observed decrease hepatic triglyceride content in those with NAFLD was not due to weight loss. This was further confirmed by a lack of relationship between the degree of weight change versus the decrease in hepatic fat content (Fig. 2D).

LPCN 1144 DECREASED MARKERS OF LIVER INJURY

At baseline, the mean values of AST, ALT, ALP, and GGT (±SD) were 18.1 (±5.5) U/L, 24.1 (±11.5) U/L, 66.3 (±18.2) U/L, and 41.2 (±51.4) U/L, respectively (Supporting Table S1). The AST and ALT values declined to varying degrees (−1 to −9 U/L for AST and −1 to −17 U/L for ALT) in about half of the study population (Fig. 3A,B). Interestingly, the ALP declined in 26 of 32 (−2 to −26 U/L) (Fig. 3C). The GGT levels declined in 20 of 32 (−1 to −137 U/L) (Fig. 3D). The mean changes in AST, ALT, ALP, and GGT from baseline in the population with NAFLD were 0.0 U/L (P = 0.51), −0.5 U/L (P = 0.56), −7.2 U/L (P = 0.90), and −8.9 U/L (P = 0.71), respectively. Although the mean changes of liver enzymes were not significant due to

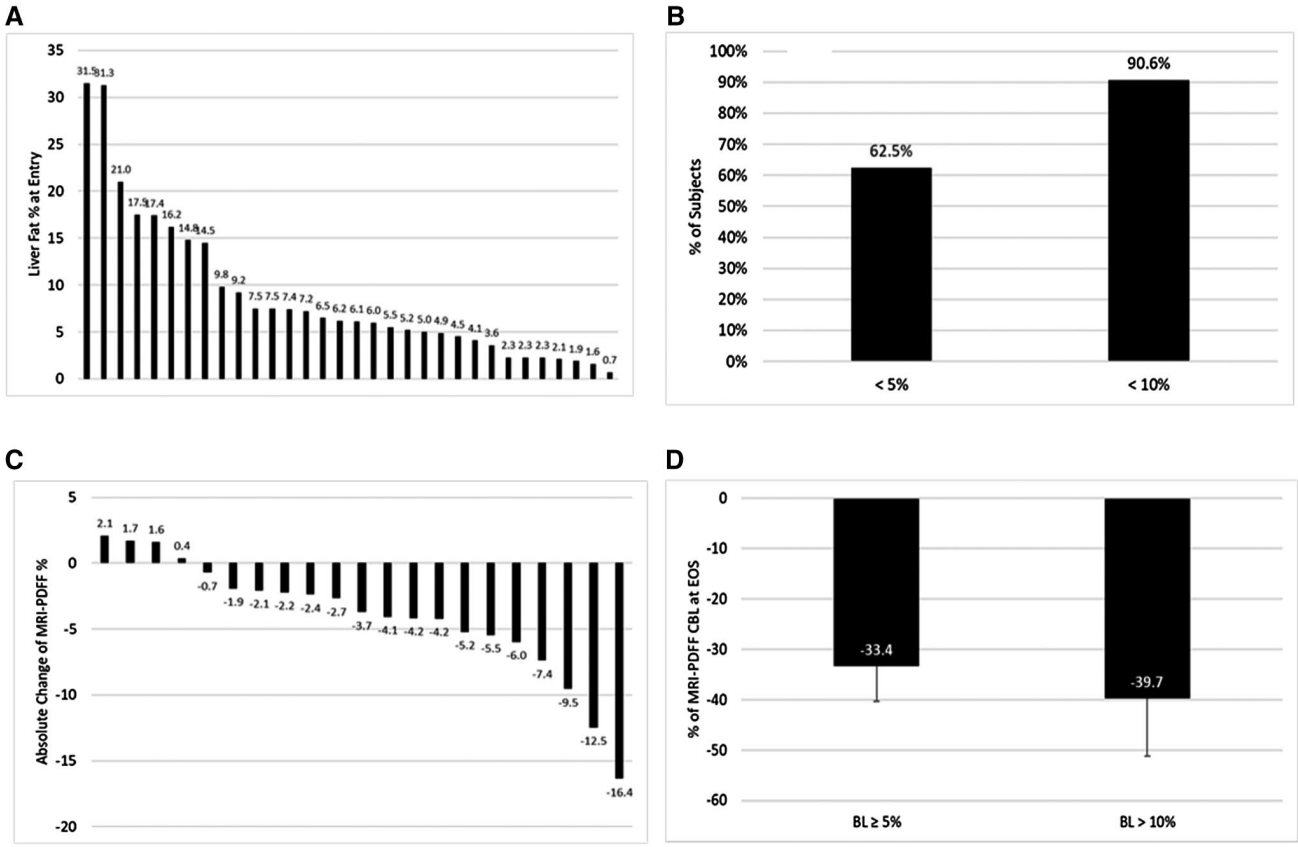

FIG. 1. Liver fat percentage distribution, correlation with BMI and ALT at baseline, and response to treatment in a population of males with low testosterone. (A) Distribution of liver fat percentage measured by MRI-PDFF at entry into the study (total n = 32). (B) Proportion of subjects (expressed as percentages) with liver fat <5% and <10% at EOS. (C) Absolute change in liver fat percentages from baseline for individual subjects with NAFLD (n = 21) at 16 weeks of treatment, reported as percentages. (D) Liver fat percentage change from baseline (expressed as percentages) for subjects with liver fat ≥5% and >10% at baseline. Abbreviation: CBL, change in baseline liver fat.

TABLE 2. MULTIPLE REGRESSION ANALYSIS OF LIVER FAT PERCENTAGE VERSUS LIVER DISEASE MARKERS

Regression Statistics						
Multiple *R*	0.60					
R^2	0.36					
Adjusted R^2	0.31					
Standard error	6.55					
Observations	32					
Analysis of variance						
	df	SS	MS	*F*	Significance *F*	
Regression	2	692.143	346.071	8.054	0.002	
Residual	29	1246.048	42.967			
Total	31	1938.191				
	Coefficients	Standard error	*t* stat	*P* value	Lower 95%	Upper 95%
Intercept	–12.548	6.218	–2.018	0.053	–25.265	0.170
ALT BL	0.259	0.106	2.443	0.021	0.042	0.476
BMI BL	0.448	0.185	2.418	0.022	0.069	0.828

Abbreviations: df, degrees of freedom; F, F-test statistic; MS, mean squares; SS, sum of squares.

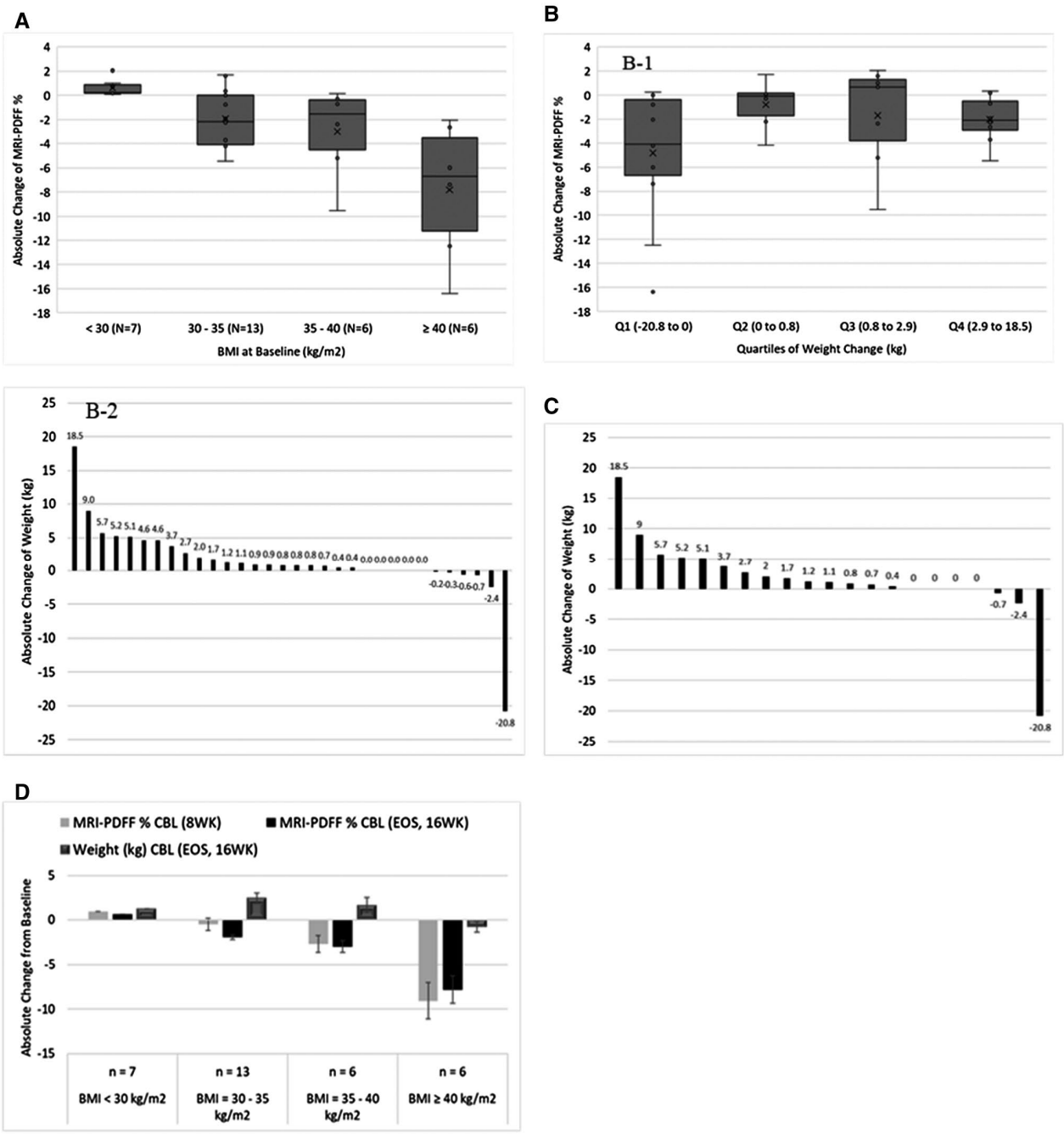

FIG. 2. Changes in liver fat percentages from baseline in relation to BMI and body weight in a population of males with low testosterone. (A) Absolute change in liver fat percentages from baseline (expressed as percentages) across quartiles of BMI at baseline in the study population. The range of BMI quartiles at baseline (kg/m^2): first quartile <30, second quartile 30-35, third quartile 35-40, and fourth quartile ≥40. (B) Changes in liver fat percentages from baseline in relation to body weight. (B-1) Absolute change in liver fat percentages from baseline (expressed as percentages) across quartiles of body-weight changes after treatment in the study population. Range of weight quartiles (kg): first quartile −20.8 to 0, second quartile 0-0.8, third quartile 0.8-2.9, and fourth quartile 2.9-18.5. (B-2) Absolute change in body weight from baseline for individual subjects within the total study population (n = 32) at 16 weeks of treatment (values reported in kilograms). (C) Absolute change in body weight from baseline for individual subjects with NAFLD (n = 21) at 16 weeks of treatment (values reported in kilograms). (D) Absolute change in liver fat percentage (MRI-PDFF) at 8 weeks (black column bar) and 16 weeks (light gray column bar) of treatment (expressed as percentages), and absolute change in body weight (dark gray column bar) from baseline (expressed as kilograms) across quartiles of BMI in the study population. The range of BMI quartiles at baseline (kg/m^2): first quartile <30, second quartile 30-35, third quartile 35-40, and fourth quartile ≥40. Abbreviation: CBL, change in baseline liver fat.

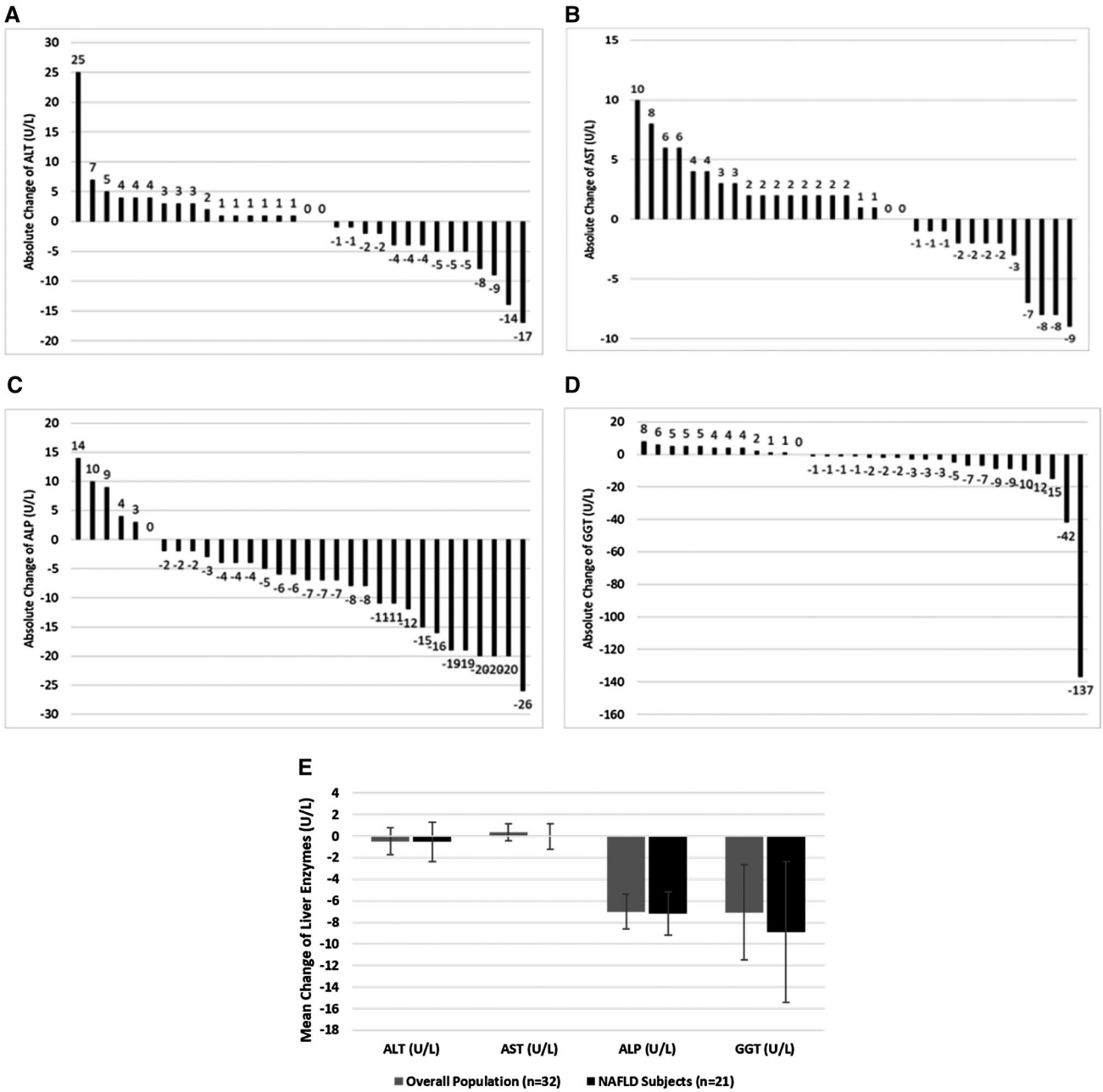

FIG. 3. Changes in liver enzyme levels from baseline after treatment for overall population of males with low testosterone and individuals with NAFLD. (A) Absolute change in serum ALT levels from baseline (expressed as U/L) for individual subjects at week 16 of treatment within the overall population (n = 32). (B) Absolute change in serum AST levels from baseline (expressed as U/L) for individual subjects at week 16 of treatment within the overall population (n = 32). (C) Absolute change in serum ALP levels from baseline (expressed as U/L) for individual subjects at week 16 of treatment within the overall population (n = 32). (D) Absolute change of serum GGT levels from baseline (expressed as U/L) for individual subjects at week 16 of treatment within the overall population (n = 32). (E) Mean absolute change of serum liver enzymes levels from baseline (expressed as U/L) for overall population (n = 32) (gray column bar) and subjects with NAFLD (n = 21) (black column bar).

low baseline, most of the NAFLD population had improvement in the reduction of liver enzymes: 43% of the subjects for AST, 48% for ALT, 86% for ALP, and 67% for GGT. The changes in liver enzymes for those with NAFLD at baseline were concordant and similar to the study group (Fig. 3E).

TABLE 3. ADVERSE EVENTS FOR LPCN 1144 TREATMENT

	MRI-PDFF Full Analysis Set (n = 32)	
AE Category	n	%
TEAE	8	25.0
Sinus infection	2	6.3
Drug-related AE	1	3.1
SAE	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TOLERABILITY AND SAFETY OF LPCN 1144

No subjects reported any serious adverse events. Eight participants reported an adverse event, which is mild or moderate (Table 3). None of these were considered attributable to LPCN 1144. Specifically, there were no instances of increase in liver enzymes that were considered suspicious for drug-induced liver injury.

Discussion

Therapeutic approaches for NAFLD continue to evolve. The ideal treatment should target biologically relevant pathways, be efficacious, safe, and easy to administer. The optimal approach should also target populations most likely to benefit from the therapeutic intervention. This study demonstrated a high prevalence of NAFLD in hypogonadal males and a remarkable improvement in both hepatic steatosis and markers of liver injury following therapy with the oral testosterone prodrug LPCN 1144. These findings have several implications for the field. It is noteworthy that two-thirds of hypogonadal individuals in this study had hepatic fat content ≥5% at baseline. This is higher than rates reported in the general population (~25%).[20] This finding raises the possibility that low testosterone directly contributes to this high prevalence. However, it should be noted that the mean BMI of this cohort was 33.8 kg/m^2 and that the proportion of individuals with NAFLD are within the range reported for an obese population.[2] The presence of hypogonadism in studies of NAFLD in obesity has not been systematically studied, and it remains plausible and possible that a low testosterone state may have contributed to the severity of the underlying steatosis based on the existing literature linking hypogonadism to obesity.[21-25]

The most noteworthy finding of this study is the decrease in steatosis after initiation of LPCN 1144. It is highly unlikely that these changes were due to changes in behavior such as adoption of a healthier lifestyle and weight loss, which are well known to result in "defatting" of the liver.[26] In fact, improvement in hepatic steatosis shown in the subjects with modest weight-gain indicates that these changes were an effect attributable to LPCN 1144.

A key element in early proof-of-concept studies is evidence that a given therapeutic intervention not only reduces steatosis but also improves liver injury. It is worth noting that the baseline liver enzyme levels for overall and subjects with NAFLD are low compared with subjects recruited in other NASH studies (i.e., normal range of ALT, AST, ALP, and GGT in our study is 6-41, 9-34, 37-116, and 11-52 U/L, respectively). Because the baseline liver enzyme levels in this study were very low, a meaningful mean decrease was not observed with LPCN 1144 treatment. However, most of the subjects in the overall population or with NAFLD experienced a decrease in liver injury markers. The observed reduction in liver enzymes further suggests that correction of a low testosterone state in hypogonadal males has the potential for improving both the underlying dysmetabolic state and resultant liver injury. Testosterone has several biological effects, including increased muscle mass, enhanced insulin sensitivity, and lipid use.[27,28] Lack of testosterone would conversely be expected to worsen insulin resistance and increase the delivery of lipotoxic lipids to the liver. The data presented here provide a rationale for studying the potential use of LPCN 1144 to both reverse hypogonadism and improve NAFLD in hypogonadal males.

There are several limitations in this early phase study. First, no histological data were available. It is therefore not possible to investigate whether LPCN 1144 replacement would resolve steatohepatitis or reduce progression to cirrhosis. However, the improvement in hepatic steatosis and markers of liver injury support the possibility that LPCN 1144 may not only improve NAFLD but improve more clinically meaningful outcomes in histologically defined populations of hypogonadal males with

NASH and clinically significant fibrosis. Second, this study was performed without placebo. Without placebo, it is hard to confirm the clinically meaningful effect of the intervention on improving NAFLD or NASH.

Another limitation of this study is the absence of data on changes in liver stiffness. Liver stiffness if often considered to reflect underlying fibrosis, but actually reflects a composite of inflammation, fibrosis, vascular congestion, and even cholestasis.[29] It has also been suggested that a decrease in steatosis may result in increase in liver stiffness in the short term.[30,31] These render any short-term changes in liver stiffness difficult to interpret, and the absence of such data should not be considered a barrier toward additional development of LPCN 1144 as a therapeutic option for NASH with significant fibrosis in hypogonadal males.

In summary, this early-phase exploratory study demonstrates that LPCN 1144 improves hepatic steatosis and liver injury in hypogonadal males. The degree of reduction in steatosis was greater in those with the higher degree of baseline hepatic fat content. Together with its safety profile in this population, these data support further studies to determine whether LPCN 1144 is of therapeutic value in hypogonadal males with NASH and clinically significant fibrosis.

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