Childhood obesity negatively influences adult Leydig cell function

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Background: Childhood obesity is a global health problem and co-morbidities develop already during childhood and adolescence. Male obesity impacts negatively on the reproductive function. Testosterone is decreased, sperm quality reduced, and the physical and molecular structure of germ cells altered in obese males. However, less is known about the role of prepubertal obesity on future reproductive function.

Objective and Hypotheses: The aim of our study was to explore the influence of prepubertal obesity on reproductive potential and androgenic status in adult male rats.

Material and Methods:
Lewis male rats were exposed to high fat diet (HFD) and standard chow (SC) from day 21 until 3 (group 1) and 9 months (group 2). Various anthropometric data including fat mass and adipocyte diameter were analyzed. Mating studies and semen analyses were performed.
Sex steroids and gonadotropin levels were determined by immunoassays.
Testis morphology was evaluated by microscopy.
Expression of Leydig-, Sertoli- and germ cell specific genes were analyzed at the transcriptional (q-PCR) level.

Results:

Figure 1

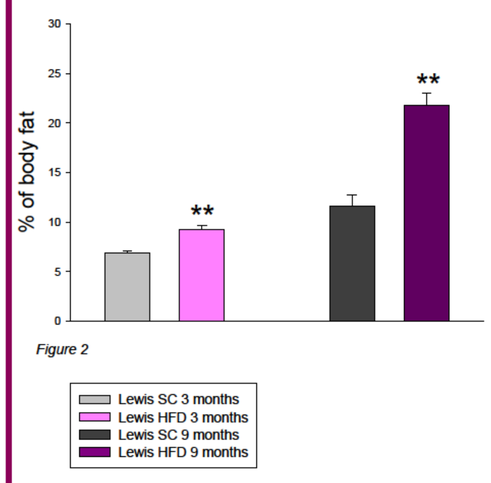

Figure 2

Adipocyte diameter in µm	Epididymal	Inguinal
Lewis SC 3 months	78.95	71.99
Lewis HFD 3 months	90.24 (p=0.019)	82.58 (p=0.037)
Lewis SC 9 months	104.45	93.89
Lewis HFD 9 months	114.80 (p=<0.001)	101.95 (p=0.348)

Table 1

As expected % body fat as measured by ECHO and adipocyte diameter significantly increased with age and between the different groups.

The ratio testis weight/body weight was reduced by 6% in group 1 but significantly by 22% in group 2 (p=0.015). Anthromopetric data including body weight, body fat, testis and epididymis weight are depicted in table 2.

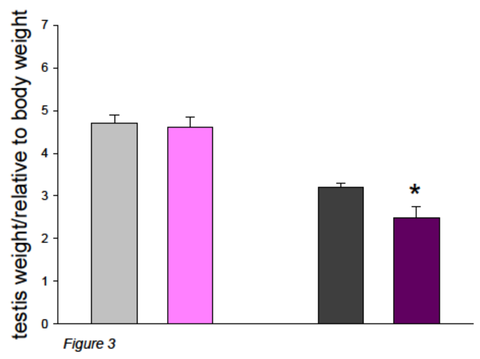

Figure 3

Anthropometric parameters	Body weight in g	Body fat in g	Testis weight in g	Epididymis weight in g
Lewis SC 3 months	357.48 +/- 26.65	26.14 +/- 3.83	1.54 +/- 0.14	0.25 +/- 0.03
Lewis HFD 3 months	381.23 +/- 11.54	38.61 +/- 3.12	1.65 +/ 0.17	0.25 +/- 0.03
Lewis SC 9 months	503.30 +/- 17.69	58.64 +/ 18.08	1.66 +/- 0.05	0.335 +/- 0.05
Lewis HFD 9 months	563.20 +/ 14.41	122.14 +/- 17.62	1.52 +/- 0.20	0.2975 +/- 0.06

Table 2

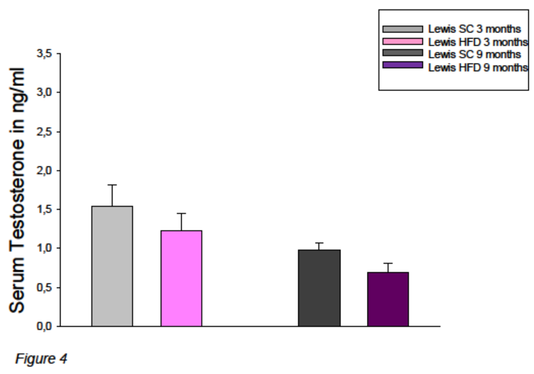

Figure 4

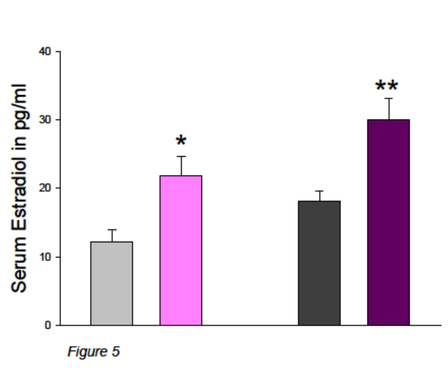

Figure 5

Serum testosterone was reduced in obese rats from group 2 by 29% (ns), while estradiol was elevated in both groups of obese animals by 44% (p=0.018) and 40% (p=0.005), respectively.

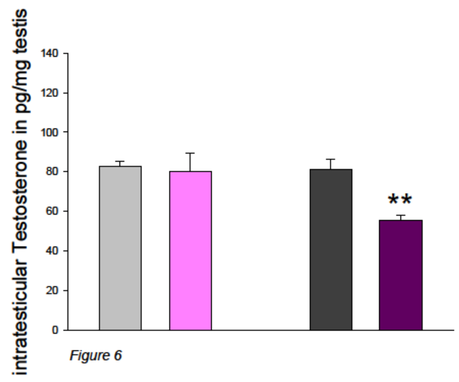

Figure 6

Intratesticular testosterone was measured and did not show significant differences in group 1 but was decreased by 31.5% (p=0.004) in group 2 (Figure 6).

We observed an upregulation of steroidogenic enzymes in group 1, while 9-months treatment with HFD (group 2) down-regulated steroidigenic enzymes (Figure7,8).

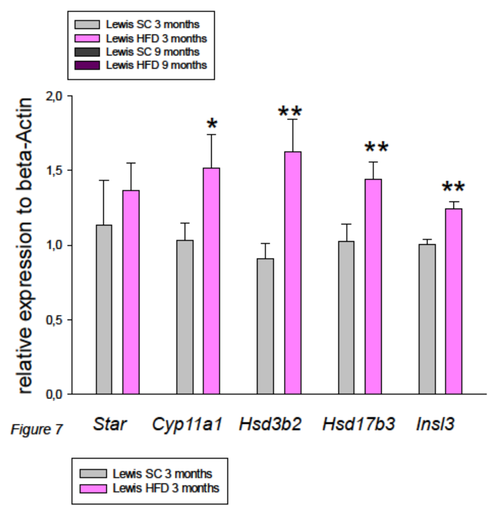

Figure 7

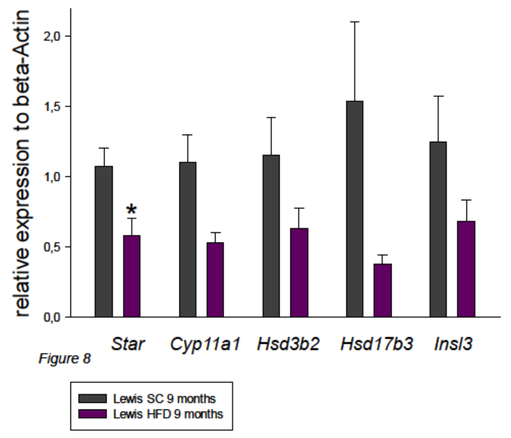

Figure 8

Mating studies at 3 months of age revealed the same amount of litters but litters from animals on HFD were 22% shorter and 10% lighter than litters from animals on SC. Sperm analysis showed a lower number of motile and progressive sperm and a higher number of static sperm. The track speed and progressive velocity was reduced by 17.9% and 16.6% respectively already in group 1 (table 3).

Sperm analysis	Lewis SC	Lewis HFD
Total	1015.5	1116.75
%Motile	38.66	35
%Progressive	12.66	10.75

Velocity distribution	Lewis SC	Lewis HFD
rapid	34.66	30
medium	4	4.5
slow	1	1
static	60.5	64

Functional analysis	Lewis SC	Lewis HFD
Path Velocity	145.18	123.025
Track speed	231.43	190.025
Lateral displacement	10.66	8.475
Progressive Velocity	96.83	80.7
Beat Cross Frequency	18.76	17.725

Table 3

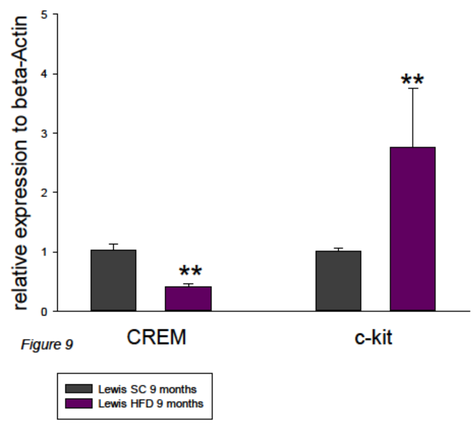

Figure 9

C-kit was significantly upregulated in obese animals from group 2 and may be a sign of premeiotic arrest, whereas CREM was downregulated as a marker of spermiogenesis (Figure 9).

Conclusion:
Long-term (9 months) obesity developed in the prepubertal period significantly suppressed Leydig cell capacity to produce testosterone and altered the T/E2 ratio in obese rats. Furthermore steroidogenic enzymes were downregulated and intratesticular testosterone significantly decreased. In addition sperm motility was negatively affected in obese animals on HFD and litters were smaller and had a lower birth weight. If translated into human medicine, the observed perturbations of sex hormone levels may indicate a disturbed spermatogenesis and attenuated reproductive potential and fertility in obese males.

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