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Obesity and Increased Risk for Oligozoospermia and Azoospermia

The global obesity epidemic parallels a decrease in male fertility. Yet, the association between body mass index (BMI) and sperm parameters remains controversial. A negative correlation between BMI and sperm concentration or total sperm count was shown by several reports[1,2] but not documented by others.[3,4] The purpose of this report was to update the level of evidence on the association between BMI and sperm count through a systematic review and meta-analysis.

Methods. A systematic review of available literature was conducted to investigate the impact of BMI on sperm count in men according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. A PubMed and EMBASE search identified relevant studies published until October 2010. Authors of relevant studies were contacted by e-mail and asked to complete a standardized data form regarding total sperm counts according to BMI categories. Unpublished data obtained from patients followed at the Infertility Center of Jean Verdier Hospital, Bondy, France, between January 2007 and December 2010 were also included.

The following BMI categories were used for analyses: lower than 18.5, 18.5 to 24.9, 25.0 to 29.9, and 30.0 or higher (calculated as weight in kilograms divided by height in meters squared). Data were stratified according to total sperm count as having normozoospermia ($\geq 40 \times 10^6$ spermatozoa per ejaculate), oligozoospermia ($< 40 \times 10^6$ but > 0 spermatozoa per ejaculate), and azoospermia (absence of spermatozoa), as specified in World Health Organization guidelines.[5] We performed random effects models to obtain summary estimates to account for interstudy variation. Studies were weighted according to an estimate of statistical size defined as the inverse of the variance of the log odds ratio (OR). Prevalent ORs and 95% confidence intervals are presented. We calculated the ORs of overweight and obese men presenting with oligozoospermia or azoospermia compared with normal-weight men.

Results. A total of 8873 articles were identified. In total, 31 articles were potentially appropriate to be included in the meta-analysis because they investigated the relationship between BMI and sperm parameters. A total of 14 eligible studies were included in the present meta-analysis, corresponding to a total study sample of 9779 individuals. Overweight men were at significantly increased odds of presenting with oligozoospermia (OR, 1.11; 95% CI, 1.01-1.20) or azoospermia (OR, 1.39; 95% CI, 0.98-1.97) compared with normal-weight men (**Figure**). Likewise, obese men were at increased risk of oligozoospermia (OR, 1.42; 95% CI, 1.12-1.79) or azoospermia (OR, 1.81; 95% CI, 1.23-2.66) compared with normal-weight men (Figure).

Comment. This meta-analysis based on 9779 men showed an inverse association between overweight or obesity and abnormal sperm count. This relationship may be explained by different pathophysiological hypotheses: (1) hypogonadotropic hyperestrogenic hypogonadism due to aromatization of steroids in estrogens in peripheral tissues[6]; (2) direct alterations of spermatogenesis and Sertoli cell function[7]; (3) hip, abdominal, and scrotal fat-tissue accumulation leading to the increase of scrotal temperature[8]; and (4) accumulation of toxic substances and liposoluble endocrine disruptors in fatty tissue.[2]

Our strategy based on individual patient data and analysis of dichotomized sperm count made it possible to have a more homogeneous meta-analysis of the available evidence. Limitations of our study are the exclusion of 15 studies because of incomplete data or lack of response from authors and the variations in the study populations. Yet, this variability suggests that our findings may

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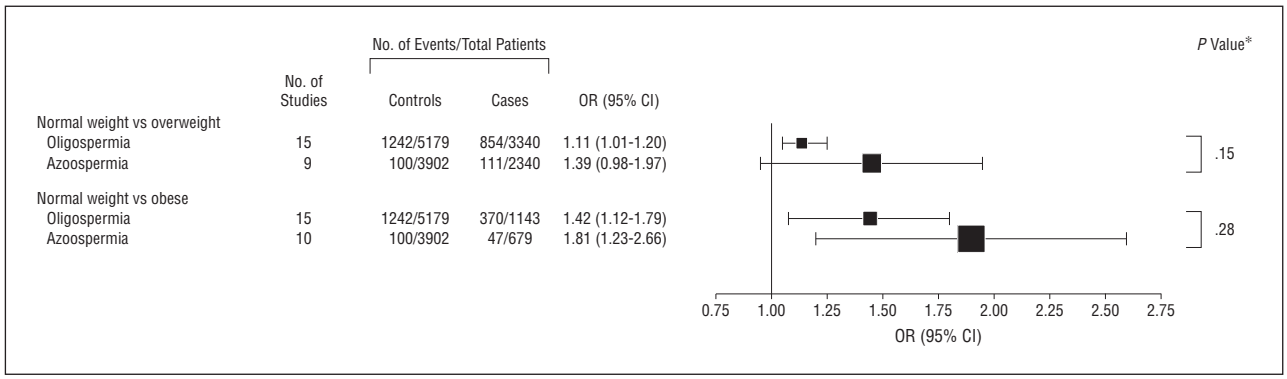

Figure. Association between oligozoospermia and azoospermia stratified by body mass index (BMI) categories. Normal weight: BMI between 18.5 and 24.9 (calculated as weight in kilograms divided by height in meters squared); overweight: BMI between 25.0 and 29.9; obese: BMI greater than 30.0. *P value for heterogeneity. OR indicates odds ratio.

be generalizable to both infertile and general population. We were also reliant on BMI and conventional semen parameters as relevant measures of body fat content and assessment of fertility potential. However, even if they may not be the best indicators, they remain the gold standard for clinical evaluation of adiposity and male fertility, respectively, and allow a clear application of our findings. On the other hand, the strengths of our meta-analysis are a large sample size based on a collection of individual level data.

In conclusion, overweight and obesity are associated with an increased risk of azoospermia or oligozoospermia. These data strongly suggest that excess body weight affects sperm production.

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Effect of Antihypertensive Therapy on Cognitive Function in Early Executive Cognitive Impairment: A Double-blind Randomized Clinical Trial

Approximately 50% of older hypertensive individuals have difficulties in executive function, the cognitive domain that controls complex tasks.[1] Hypertensive individuals with executive dysfunction have a high rate of conversion to dementia.[2] To our knowledge, to date, no study has investigated therapeutic options for executive dysfunction. Recent evidence suggests that the renin angiotensin system plays a central role in linking hypertension to cognitive function, offering new therapeutic options for cognitive protection.[3] In the brain, angiotensin receptor blockers (ARBs) block the type 1 but not the type 2 receptor, whereas angiotensin-converting enzyme inhibitors (ACEIs) decrease activation of both receptors. Activating the type 2 receptor may provide cognitive protection.[4] We therefore hypothesized that an ARB-based regimen would be superior to other antihypertensive regimens in cognitive protection, especially executive function, and conducted a 12-month double-blind randomized clinical trial comparing candesartan, lisinopril, and hydrochlorothiazide in hypertensive individuals with early executive dysfunction.

Methods. The study design is fully described elsewhere.[5] Subjects were recruited from the greater Boston area, Massachusetts, and were 60 years or older, had hypertension (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg), and demonstrated evidence of executive dysfunction based on the executive clock draw test (CLOX1 score <10). We excluded those with a Mini-Mental State Examination (MMSE) score lower than 20 or those with a clinical diagnosis of dementia, diabetes mellitus, stroke, or congestive heart failure. Antihypertensive medications were tapered using a standard protocol described elsewhere.[5] Randomization using a computer-generated random allocation sequence occurred after baseline data collection, and participants were seen every 2 weeks until their blood pressure was controlled (<140/90 mm Hg). Participants were treated with escalating doses of lisinopril, candesartan, or hydrochlorothiazide to achieve a blood pressure lower than 140/90 mm Hg. Long-acting nifedipine and long-acting metoprolol succinate were added if the goal blood pressure was not achieved. Cognitive assessments were repeated at 6 and 12 months and included Trail-Making Test (TMT) parts A and B, which assesses executive function; Hopkins Verbal Learning Test–Revised (HVLT), which assesses memory; and the Digit Span Test, which assesses attention. The Hebrew SeniorLife institutional review board approved the study, and written informed consent was obtained. An intention-to-treat analysis was performed, and linear mixed models for repeated measures were used to compare the progression of cognitive outcomes in the 3 groups. Least-square means adjusted for age and baseline MMSE score were computed for each visit by treatment group.

Results. Of the 63 eligible individuals screened, 53 stopped their antihypertensive medications and were randomized to lisinopril (n=18), candesartan (n=20), or hydrochlorothiazide (n=15); 47 completed 6 months, and 31 completed 12 months. A sample description is provided in the eTable (http://www.archinternmed.com). The number of subjects achieving blood pressure control were similar (lisinopril, 91%; candesartan, 100%; and hydrochlorothiazide, 100%; $P=.40$) and systolic blood pressure reductions were similar in all 3 groups (mean [SD] reduction was 28 [5] mm Hg for lisinopril, 27 [5] mm Hg for candesartan, and 21 [5] mm Hg for hydrochlorothiazide; $P=.75$). There were no differences in the reported adverse events between the 3 groups. After adjusting for age and baseline MMSE score, those randomized to candesartan demonstrated the greatest improvement in TMT part B ($P=.008$); the adjusted TMT (parts A and B), which adjusts the test for motor speed ($P=.01$); and the recognition portion of the HVLT ($P=.03$) (**Figure**).

Comment. This study suggests that ARBs are associated with improvement in executive function in older hypertensive adults with early executive cognitive impair-

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