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Sub-Albuginean Adipocyte Accumulation is Associated with Erectile Dysfunction: First Clinical Evidence and Pathophysiological Implications

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Abstract

The aim of this study is to determine the presence of adipocyte accumulation under penile tunica albuginea in a group of refractory erectile dysfunction patients. Nineerectile dysfunction patients (case group) and eleven potent patients with Peyronie's disease (control group) underwent penile prosthesis implantation and curvature correction surgeries, respectively. In both groups, sub-albuginean tissue samples were taken within the operative time. Groups were compared in terms of clinical characteristics, co-morbidities and presence of sub-albuginean adipocyte accumulation. Of the nine patients in the case group, eight presented cavernous fat cell accumulation, while only one patient in the control group presented this finding ($p<0.05$). A significant association ($p<0.05$) was found between adipocyte accumulation and erectile dysfunction (OR 35 CI 95% 1.98-1727.62). A similar association with chronic arterial hypertension was also found (OR 20 CI 95% 1.29-1008.46). This is the first human study to report an association between erectile dysfunction and penile sub-albuginean fat accumulation. Metabolic syndrome-related conditions could cause disruption in androgen homeostasis, leading to adipocyte accumulation. Venous leakage secondary to accumulation of fat under tunica albuginea could be an important element in the pathophysiology of erectile dysfunction, especially in metabolic syndrome patients that do not respond to medical therapy.

Keywords: Erectile dysfunction; Androgens; Metabolic syndrome

Introduction

Erectile function depends on the interaction of psychological factors and an appropriate balance between the endocrine and nervous systems, together with an adequate vascular bed [1]. Disruption of any of these elements could impair normal erections.

In last years, different authors have presented androgens as cornerstones of this complex neurophysiological process [2-4]. Testosterone may play a pivotal role in maintaining penile nerve, smooth muscle and endothelium structure and function; maintaining tunica albuginea structural integrity and connective tissue matrix fibroelastic properties; and regulating differentiation of cavernous pluripotent cells into trabecular smooth muscle [1].

Several studies have shown that patients not responding to oral Phosphodiesterase 5 Inhibitors (PDI5), especially those affected by Metabolic Syndrome (MS), may have a quantitative or qualitative alteration in androgen metabolism [2-5]. Currently, obesity and MS related androgen alterations are thought to play a pivotal role in the pathophysiology of Erectile Dysfunction (ED) [4-6].

The role of androgens in the differentiation of pluripotent sub-albulginean cells into trabecular smooth muscle has been poorly studied. Traish et al. in an animal model have shown that hypogonadism secondary to surgical castration produces severe ED associated with replacement of normal smooth muscle by adipocytes, in the penile sub-albuginean region [7]. Adipocyte accumulation is thought to impair penile vascular bed performance, leading to venous leakage and lack of normal [1,5,7].

We hypothesized that penile sub-albuginean fat accumulation is associated to refractory ED. Venous leakage secondary to fat cell accumulation under tunica albuginea may play a pivotal role in the pathophysiology of this disorder. In the present study, we compared the histology of the penile sub-albuginean region of refractory ED patients undergoing penile implant surgery and potent patients with Peyronie's disease undergoing curvature correction procedures.

Materials and methods

Patients

This study has been performed according to the Declaration of Helsinki and was approved by FundacióPuigvert ethics committee. Informed consent was obtained from every patient. Between May 2009 and June 2011, twenty patients were recruited. Inclusion criteria included men with severe ED not responding to PDI5, intracavernous/intraurethral alprostadil and vaccum assisted therapy with indication for penile implant surgery (case group) and potent men with stable

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Peyronie's disease not responding to medical therapy with indication for penile curvature correction surgery (control group). Potency was measured using the International Index of Erectile Function (IIEF-5) Questionnaire. The self-reported IIEF-5 score for the case and control group was 22-25 and 5-7, respectively.

Exclusion criteria included previous pelvic/genital surgery; previous oncologic treatment of pelvic neoplasms; known neurologic, vascular or endocrine disease and a specific treatable cause of ED.

For each patient, personal information and clinical conditions were documented. Age, Body Mass Index (BMI) and presence of specific co-morbidities, such as chronic arterial hypertension, type 2 diabetes mellitus, dyslipidemia and smoking (defined as more than 1 cigarette per day) were recorded.

Surgical procedure and tissue sampling

Nine and eleven patients were subjected to penile prosthesis implantation or curvature correction surgery, respectively. Only local anesthesia was used. During the procedures, the same surgeon performed cold-knife resection of one sub-albuginean tissue sample measuring 1 cm^2. The sample was harvested from the site of the original incision, that is, the site of the prosthesis implantation (case group) or the site of the plaque excision (control group). The samples were then fixated with 10% formalin and sent to the pathologist. There were no intra or postoperative complications, and every patient was discharged the same day of surgery.

Histological evaluation

The sub-albuginean samples were cut into 2-4 mm thick sections, and then fixated in phosphate buffer and embedded in paraffin for subsequent staining with hematoxylin and eosin. Later, the uro-pathologist analyzed each section, searching for adipocyte-like images under tunica albuginea. When using this staining procedure, adipocytes appear like empty cellular structures in which fat has been washed out [7]. When this image was found in close relation with tunica albuginea, the sample was defined as positive for adipocyte accumulation.

Data analyses

A bivariate analysis was performed. Inter-group difference was studied using Wilcoxon signed-rank test for age and BMI (results were presented as medians, with ranges between the 25th and 75th percentiles) and Fisher's exact test for sub-albuginean adipocyte accumulation, chronic arterial hypertension, type 2 diabetes mellitus, dyslipidemia and smoking. The unadjusted Odds Ratios (OR) and their corresponding 95% Confidence Intervals (CI) were calculated. P value <0.05 was considered significant in every analyses.

Category	Control group	ED group	P value
Age (years)	57 (55-64)	58 (55-61)	0.849
BMI (kg/m^2)	24.7 (23.1-26.4)	28.1 (26.1-30.1)	0.004
Chronic arterial hypertension (n)	1 (9.1%)	6 (66.7%)	0.012
Type 2 diabetes mellitus (n)	3 (27.3%)	5 (55.6%)	0.205
Dyslipidemia (n)	3 (27.3%)	6 (66.7%)	0.095
Smoking (n)	4 (36.4%)	5 (55.6%)	0.342
Adipocyte accumulation (n)	1 (9.1%)	7 (77.8%)	0.003

ED: Erectile dysfunction; BMI: Body Mass Index

P<0.05 is considered significant

Table 1: Clinical characteristics and histologic findings comparison between Control and ED group.

Category	Unadjusted OR	95% CI	P value
Age >60 years	1.5	0.10-21.31	0.765
BMI > 25 kg/m^2	6.13	0.62-81.13	0.064
Chronic arterial hypertension	20	1.29-1008.46	0.007
Type 2 diabetes mellitus	3.33	0.37-32.25	0.199
Dyslipidemia	5.33	0.58-54.82	0.078
Smoking	2.19	0.26-18.82	0.391
Adipocyte accumulation	35	1.98-1727.62	0.002

ED: Erectile dysfunction; OR: Odds Ratio; CI: Confidence Interval

P<0.05 is considered significant

Table 2: Adipocyte accumulation and clinical characteristics unadjusted Odds Ratios for presenting refractory ED.

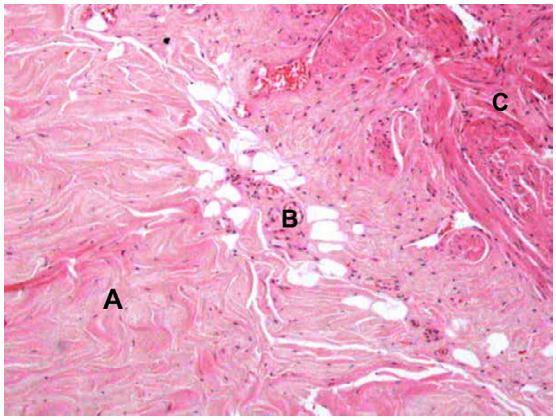

Figure 1: Hematoxilin and eosin stained cavernous sample showing tunica albuginea **(A)** sub-albuginean adipocyte accumulation **(B)** and trabecular smooth muscle **(C)** Magnification 125X.

Results

Clinical characteristics and histologic findings, for both ED and control groups, are presented in Tables 1 and 2. Of the nine patients undergoing surgery for severe ED, 78% presented cavernous fat cell accumulation when analyzed by the pathologist. Adipocyte accumulation was diagnosed by identifying empty cellular clusters under tunica albuginea, as seen in Figure 1. Only one patient in the control group showed the same finding. Median BMI was approximately 28 kg/m^2 and 25 kg/m for the ED and control group, respectively (p<0.05). Sub-albuginean fat accumulation and chronic arterial hypertension were found to be significantly associated to ED, with OR of 35 (CI 95% 1.98-1727.62) and 20 (CI 95% 1.29-1008.46), respectively (p<0.05).

Discussion

Adipocyte accumulation was significantly higher in ED patients compared with potent patients. In this specific study, unadjusted Odds Ratio calculation showed, that is 35 times more likely to present severe ED if a patient has cavernous fat cell accumulation. Cardiovascular risk factors, such as increased BMI and chronic arterial hypertension, were also significantly higher in the ED group. Other clinical characteristics were also more prevalent in the case-group, but the differences were not significant; sample size may be in part accountable for this fact.

Different studies have shown that the differentiation of pluripotent cells into trabecular smooth muscle is androgen dependent [1,8,9]. Traish et al. demonstrated that orchiectomized rabbits and rats

presented severe ED associated with fat cell accumulation under the tunica albuginea; while sham operated animals' maintained potency and presented normal trabecular smooth muscle in the cavernous samples. Additionally, when testosterone replacement therapy was given, histological changes were reverted and trabecular smooth muscle normal appearance was restored [7,10]. Simon et al. showed that the administration of flutamide (a known anti-androgen) or a gonadotropin releasing hormone antagonist to neonatal rats produces significant reduction in penile length and weight, together with penile fat accumulation [11].

Androgens play multiple roles in the different mechanisms that allow a normal erection; while its role in maintaining erectile tissue architecture and modulation of neural function and structural integrity of the smooth muscle, endothelium, and connective tissue matrix have been widely studies ; its role involving cellular differentiation and muscle lineage activation has been recently postulated [1,8,9,11-15].

Different authors have shown important changes in corpora cavernosa architecture in hypogonadic animals [7,16-19]. It has been demonstrated that estrogen administration inhibits androgen metabolism and therefore disrupts androgen dependent smooth muscle proliferation. Goyal et al. have revealed that estradiol and diethylstilbestrol administration reduces plasma testosterone levels and produces accumulation of adipocytes in the corpora cavernosa of mature animals [16-19]. Furthermore, the administration of bisphenol A (another agent with estrogen activity) to rabbits also produces severe ED, together with fat replacement of normal sub-albuginean tissue [20]. Mansour et al. showed that the administration of diethylstilbesterol to neonatal rats induces penile adipogenesis and infertility [21].

Androgens are thought to promote differentiation of pluripotent stem cells into a muscle lineage and inhibit their differentiation into an adipocyte lineage. Also, novel studies have shown that mature differentiated smooth muscle cells, in a low testosterone environment, may suffer apoptosis and trans or de-differentiation into adipocytes [5,8,9].

Androgens, specially testosterone and dihydrotestosterone, may act on cavernous stromal cells, activating molecular pathways that lead to smooth muscle precursor cells proliferation that later differentiate to mature trabecular smooth muscle [5]. In a normal testosterone-rich environment, androgen modulation over stromal pluripotent cells activates the synthesis of α-actin, desmin, laminin, myosin and vinculin; all of which are important structural and functional elements of mature smooth muscle cells [5]. On the other hand, when there is a disruption in testosterone metabolism, myogenic apoptosis is triggered and other molecular pathways are activated in which adipogenic markers such as PPAR-g2, C/EBPa and lipoprotein lipase are up-regulated [5,22,23].

Traditionally, the link between MS and ED has been endothelial dysfunction. However, novel studies have showed that penile histologic alterations secondary to androgen disruption also play an important role in this setting [5,7,13]. Several studies have demonstrated the relationship between MS, obesity and testosterone metabolism disruption [13,24,25]. Studies have shown low levels of total and free testosterone in men presenting obesity/MS. Moreover, weight loss has been linked to an increase in circulating androgens [13,25].

The pathophysiology of MS-linked hypogonadism is not completely elucidated, though four pathways have been postulated [24]. Insulin stimulates testicular androgen biosynthesis; hence, insulin resistance seen in these patients is probably involved in the disruption of testosterone metabolism [24,26]. Various studies have exhibited that leptin is increased in MS/obese patients. Testicular tissue expresses leptin receptors that, when stimulated, inhibit leydig cells-mediated androgen synthesis. Additionally, leptin resistance or leptin insufficiency at the hypothalamus may also be involved in testosterone metabolism disruption [27].

As has been extensively established, aromatase levels are greatly increased in aMS/obesity context. This enzyme lowers testosterone levels by catalyzing the conversion of testosterone to estradiol, which in turn, through negative feedback inhibits the hypothalamus-pituitary-testicular axis that further decreases androgen levels [24]. Finally, adipocyte-produced inflammatory cytokines are known to modify normal endocrine homeostasis. Morales et al. showed that tumor necrosis factor α-intratesticular delivery decreased human chorionic gonadotropin-stimulated testosterone production [24,28].

Diabetes mellitus, chronic arterial hypertension, dyslipidemia, obesity and other chronic disorders are involved in endothelial and neural-dysfunction, both of which play an important role in ED pathophysiology [6,24]. However, these conditions may be also involved in the disruption of normal cavernous/penile fibroblastic properties through androgen metabolism alteration, as presented previously [1,6].

Restricted sample size and lack of testosterone measurement are considerable limitations of the study. Nevertheless, it should be highlighted that this is the first evidence of sub-albuginean fat cell accumulation in men presenting ED; past evidence was only based in animal models, with fewer subjects.

MS refers to the co-occurrence of several known cardiovascular risk factors. It has several definitions published by different groups. In all of them hyperglycemia, dyslipidemia, hypertension and abdominal obesity are present [29].

In this study, we could not find any relationship between MSratio and adipocyte accumulation because we did not consider all of the elements included in the cluster. This is an important limitation of the study. We hope to incorporate all of the variables in future publications.

In conclusion, this is the first study in humans to report an association between erectile dysfunction and penile sub-albuginean fat accumulation. As hypothesized by other authors, we believe that venous leakage secondary to accumulation of fat under tunica albuginea of the penis may be an important element in the pathophysiology of ED, especially in patients that do not respond to oral or intra-cavernoustherapy.

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