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Glycosylated hemoglobin (HbA1c) as a risk factor for penile implant infection: A prospective controlled trial in a tertiary center

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Abstract
Background: Penile implant infection is a devastating complication of penile prosthesis (PP) surgery. Diabetes mellitus (DM) is a major risk factor for PP infection. Yet, the incidence of PP infection among controlled diabetics is a matter of debate. We aimed in this study to evaluate the role of HbA1c level as a risk factor for PP infection.
Methods: 68 adult patients with refractory ED were prospectively enrolled and scheduled for PP insertion. They were divided into 2 groups: Group A (37 diabetic patients), subdivided into 2 subgroups according to HbA1c level, Subgroup A1 (19 patients, Good control (HbA1c less than 7%), and Subgroup A2 (18 patients, Fair control (HbA1c 7-8%). Group B included (31 non diabetic patients). The patients in both groups were compared as regards: operative time, infection rate, and other complications.
Results: The age of patients ranged from 32 to 70 years. The mean operative time in groups A and B was 54.73 ± 8.33 and 52.58 ± 8.15 minutes, respectively (p=0.289). Post-operative infection occurred in 3 patients (8.1%) in group A (all of them were in subgroup A2), and only one patient in Group B (3.2%) (p=0.620). Small subcutaneous hematoma developed in 3 patients in group A and in one patient in group B. 62 patients (91.2%) were satisfied and 6 (8.8%) were dissatisfied (3 patients in each group).
Conclusions: PP insertion is a safe option for treating ED not only in non-diabetic patients but also in controlled diabetic patients.

Keywords: Erectile dysfunction, HbA1c, infection, penile prosthesis

1. Introduction
The inability to achieve or maintain an erection powerful enough to engage in sexual activity is known as erectile dysfunction (ED) [1]. ED, which has a reported incidence of up to 50%, is one of the most unsettling consequences of diabetes mellitus in males and this association could be explained by the impaired microcirculation and neuropathy in diabetic populations [2].

In patients with ED that does not respond to, or unwilling to continue with medications, penile prosthesis (PP) is typically regarded as a "last resort" therapeutic option. High satisfaction rates of 80 to 90% were achieved in the last 40 years as a result of numerous advancements in surgical and material methods [3, 4]. Nevertheless, complications do arise and can range from 7 to 20% [5], with the majority being related to erosion, infection, and mechanical failure.

Diabetes patients are more likely to contract an infection due to microangiopathy and leucocyte dysfunction. Evidence suggests that patients with DM had a three-fold increased risk of PP infection than patients without the disease. Others have found no difference, and it is still debatable whether DM raises the risk of infection [6, 7]. Recent researches have also connected a higher risk of PP infection to poor diabetic control, as shown by increased HbA1c values. According to a multi-center study by Habous *et al*., an infection was predicted with a sensitivity of 80% and a specificity of 65% at a threshold HbA1c level of 8.5% [8].

Herein we aimed to address the role of HbA1c level as risk factor for PP infection and comparing the infection rate in controlled diabetic and non-diabetic patients.

2. Patients and Methods

2.1. Type of study and patients' recruitment

After the approval of our local ethical committee (code = 33311/08/19), 68 adult patients with refractory ED were prospectively enrolled in our study during the period from October 2019 and December 2021 in the andrology unit, Urology department, Tanta University Hospitals. A detailed consent was signed by all the patients. The patients were divided into two groups based on the HbA1c level as follows: Group A (37 diabetic patients), subdivided into 2 subgroups according to HbA1c level, Subgroup A1 (19 patients, Good control (HbA1c less than 7%), and Subgroup A2 (18 patients, Fair control (HbA1c 7-8%). Group B included (31 non diabetic patients) as a control group. We excluded patients who had other risk factors for penile implant infection such as: previous penile surgery, active infections, and other medical comorbidities (hepatic failure, and cancer patients).

2.2. Patients' evaluation

All the participants were assessed by full history taking, and complete examination. Laboratory assessment included routine laboratory investigations and hormonal profile such as serum testosterone and FSH, LH, Prolactin and E2 when indicated (in low serum testosterone level). First-morning spot mid-stream urine sample was examined to exclude UTI. Penile Doppler US was done for all patients to document presence and degree of vascular erectile dysfunction.

2.3. Surgical technique

2.3.1. Preoperative measures

We followed the rules and guidelines of infection control protocol in our center which are consisting of cleaning the operating room with antiseptic solutions before the surgery and instruct the patients to take a nighttime shower with antibacterial soap the night before surgery.

All the patients received spinal anesthesia and were positioned in supine decubitus. IV Gentamycin was given (3 mg/kg) 2 hours preoperatively and 1 gm IV ceftriaxone was administered at anesthesia induction. Shaving of suprapubic area, scrotum and upper part of thighs had been done. Sterile saline was used to rinse the hair and with use of antiseptic (Betadine shower 7.5%) for rubbing genital area, suprapubic area, upper thighs had been done for 20 minutes in a one direction circular manner then use of sterile saline for washing all this area.

2.3.2. Penile Implant Surgery

Skin sterilization was performed with povidone-iodine-based solution (10%) from the level of umbilicus till the knees of the patient before the surgery then, sterile surgical draping and insertion of Foley's urethral catheter (14 or 16fr) was done. One vial of vancomycin 500 mg and another of gentamicin 80 mg were added to 500 cc of saline and this solution was used for irrigation of the prosthesis and tissues and the storage of the dilators. The procedure started with a transverse penoscrotal incision followed by dissection through the Dartos fascia was done till exposure of corpora cavernosa. Two stay sutures were placed at the tunica of each corpus cavernosum, and then a longitudinal incision at each corpus cavernosum was done. Metal dilatation had been done till the level of glans penis distally and the pubic bone proximally using Hegar dilators up to 13 mm diameter for creation of the space for the implant. Irrigation with the antibiotic fluid had been done after each step of dilatation and before implant insertion. Trimming the penile implant according to the length of each corpus cavernosum measured. We used for all patients (Rigicon® Rigi10™ Hydrophilic Malleable Penile Prosthesis Wellkang Ltd., Harley Street, London, UK). Corporotomy closure was done using 2-0 vicryl sutures, then closure of Dartos' fascia and skin using 3-0 Vicryl sutures. Sterile dressing and elastic bandage were used to cover the wound.

2.4. Post-operative care and follow up

Overnight hospitalization was followed in our patients and after that, patients were discharged after urethral catheter removal. Oral antibiotics and NSAIDS were given for 10-14 days. Follow up visits to detect any signs of infection was considered and then a visit after 6 weeks to teach the patients how to use the prosthesis properly.

2.5. Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Number and percentage were used to describe qualitative data. The range (minimum and maximum), mean, and standard deviation were used to characterize quantitative data. Chi-square test used for categorical variables, to compare between various groups. When more than 20% of the cells have an expected count of less than 5, Fisher's Exact or Monte Carlo adjustment is performed. A P value of less than 0.05 was deemed significant.

3. Results

A total of 68 male patients with ED underwent penile prosthesis implant were included and evaluated in this study. The age of patients ranged from 32 to 70 years, and the mean of age in groups A and B was 53.41 ± 8.14 and 59.84 ± 8.32, respectively. The mean of BMI in Group A was (27.93 ± 2.39) and in Group B was (28.84 ± 2.15). Regarding the comorbidities, 37 patients were diabetic (group A) and 31 patients were not diabetic (group B), the duration of DM was more than 5 years in 23 patients (8(42.1%) in subgroup A1 and 15 (83.3%) in subgroup A2). Hypertension was reported in 16 patients in both groups, CKD in 2 patients in group A, and ischemic heart disease documented in 3 patients in group A. The mean operative time in group A and B was 54.73 ± 8.33 and 52.58 ± 8.15 minutes, respectively (p=0.289). One patient (1.5%) in Group B developed intra-operative corporal perforation and the implant was repositioned without any problems. Post-operative infection occurred in 3 patients (8.1%) in group A (all of them were in subgroup A2), and only one patient in Group B (3.2%) developed infection (Table 1). All the cases had superficial infection that was treated conservatively except one patient in group A necessitated the extraction of the implant. Small subcutaneous hematoma developed in 3 patients in group A and in one patient in group B, all of which were resolved spontaneously. According to VAS score all patients had mild to moderate pain while there was 1 patient in Group B had severe post-operative pain. In a univariate logistic regression analysis of the parameters

linked to the increased infection risk, the operative time was the only predictor (p = 0.035, OR (95% C.I) = 1.190) (Table 2). As regards the patient satisfaction, 62 patients (91.2%) were satisfied and 6 (8.8%) were dissatisfied (3 patients in each group).

4. Discussion

Penile implant is a well-established treatment of refractory ED. Throughout the past 40 years, advances in surgical techniques, and materials have continued to lower patients' morbidity and improve their satisfaction [1, 2]. Despite, PP infection is one of the most ruinous complications among diabetic patients; the studies exploring the association of HBA1c level with the infection rate are scarce. Early in the new millennium, antibiotic-enhanced prostheses were released that resulted in a significant drop of 10-year infection rates from 3-5% to 1-2% [9-13].

In the current study, three cases (4.4%) in diabetic group had post-operative infection and all of them were from Subgroup A2 (HbA1c 7-8%), while no patients in Subgroup A1 of good controlled diabetic control got an infection. On the other hand, one patient (1.5%) in Group B (non-diabetic) had infection (higher rate of infection in diabetic group but without statistical significant difference between both groups). The first study in the literature discussed this vital association was conducted by Bishop *et al.* [14] on 90 patients (32 diabetics, and 58 non-diabetics). Depending on whether their HbA1c level was over or under 11.5%, diabetic patients were split into 2 subgroups. A total of 5 patients, 4 of whom had a HbA1c above 11.5% and all of whom had diabetes, experienced prosthesis infections. The authors advised against performing penile prosthesis surgery on individuals with HbA1c levels above 11.5% and instead suggested referring them to a primary care team [14]. On the other hand, Wilson *et al.* [6] re-examined this issue and found that an HbA1c >11.5% was not predictive of infection in 389 patients undergoing penile prosthesis implantation. However, Wilson *et al*. revised their results in 1998, adding a total of 657 patients (170 diabetics, and 487 non-diabetics). The authors reported that HbA1c remained unassociated with infection despite the new data showing a significant difference between the infection rate in diabetics and non-diabetics (8.8% vs 4.1%). [15] Moreover, Madbouly *et al.* [16] in 2017 performed a retrospective study conducted on 54 elderly patients underwent PP insertion. In their multivariate analysis, HbA1c was identified as a major risk factor for infectious complications. Patients who had PP infection had an average HbA1c level of 9.1%, compared to 7.5% for those who did not. [16] Similarly, Habous *et al.* [8] in 2018 who released the largest study on 904 patients having PP insertion, revealed that patients with a HbA1c threshold of 8.5% can be identified as having a higher risk of prosthesis infection.

On the contrary, Osman *et al.* [17] in their retrospective study, observed no correlation between preoperative HbA1c and post-prosthesis infection. Similarly, Canguven *et al.* [18] in their study found that only two patients experienced infection, and that both had diabetes with HbA1c values below 9%. HbA1c was not only unrelated to infection, it was actually lower in the infection group than in the group without an infection (7.0% ± 0.14 versus 7.6% ± 1.9).

The mean operative time in the current study in groups A and B was 54.73 ± 8.33 and 52.58 ± 8.15 minutes, respectively (p=0.289). Habous *et al.* [8] found that the average operative time was 77 (44-143) minutes for an inflatable device and 35 (18-118) minutes for a malleable device. Interestingly, in our study we found a notable association between operative time and the risk of infection, the mean operative time was 70.0 ± 5.0 minutes in infected patients versus 53.0 ± 7.59 minutes in non-infected patients(p= 0.011), this means that the longer the operative time, the higher risk of infection after penile implant surgery. Furthermore, we found in the current work that the operative time was the only predictor (p = 0.035, OR (95%C.I) = 1.190) for PP infection in univariate logistic regression analysis of the parameters related to increased risk of PP infection.

Regarding the minor postoperative complications in our study, 4 patients (3 in group A and 1 in group B) developed small penoscrotal haematoma that were managed conservatively. Two patients in Group A (5.4%) and one patient in Group B (3.2%) had superficial wound infections. All of these minor complications resolved conservatively without the need of surgical intervention. Similarly, Minor complications documented by Minervini A *et al.* [19] included 10 penoscrotal haematomas (2%), 14 cases of urinary retention (3%), and 32 cases of superficial wound infection (6%); all of these minor complications were handled conservatively. A combination of factors, including good surgical methods, high volume surgeons, short operative time, and medical care focused on prevention and control of infection, may have contributed to the decreased infection rate and other complications in our study.

Regarding patient's satisfaction rate in our study, 62 patients (91.2%) were satisfied and 6 patients (8.8%) were dissatisfied (3 patients in each group) (p= 0.409). This satisfaction rate was consistent with many previous studies [18, 19]. Also, as we did not assess partner satisfaction in this study, future research should take this matter into account.

This study had some points of strength such as the prospective controlled design. However it had also some limitations. The small sample size doesn't provide sufficient statistical power. Therefore, larger scale prospective researches with extended follow up are required to support our results.

Table 1: Peri-procedural outcomes in both groups.

Variables	Group(A) (n = 37)		Group(B) (n = 31)	P value
Operative time (in minutes)				
Mean ± SD.	45.0 – 75.0		45.0 – 70.0	
Min. – Max	54.73 ± 8.33		52.58 ± 8.15	0.289
Intra-operative complications				
No	37 (100%)		30 (96.8%)	
Yes	0 (0%)		1 (3.2%)	^{FE}p=0.456
	3 of 37 (8.1%)		1 of 31 (3.2%)	^{FE}p= 0.620
Post implant Infection				
No	Subgroup A2 (n = 18)	Subgroup A1 (n = 19)	30(96.8%) 1 (3.2%)	^{MC}p= 0.083
Yes	19 (100%) 0 (0.0%)	15 (83.3%) 3 (16.7%)		
Subcutaneous hematoma	3(8.1%)		1(3.2%)	^{FE}p=0.620
Severe post-operative pain	0(0%)		1(3.2%)	^{FE}p=0.456
Patient satisfaction				
Satisfied	34 (91.9%)		28 (90.3%)	0.40905
Dissatisfied	3 (8.1%)		3 (9.6%)	

FE: Fisher Exact SD: Standard deviation
p: p value for comparing between the studied groups

Table 2: Univariate logistic regression analysis for the parameters affecting infection occurrence

	P	OR (95% C.I)
Age	0.249	0.917(0.791–1.063)
BMI (kg/m2)	0.857	0.949(0.534–1.685)
Other comorbidities		
HTN	0.680	1.897(0.090–39.817)
CKD	0.999	–
Asthmatic	1.000	–
IHD	1.000	–
HTN & CKD	0.111	21.058(0.494–897.923)
Operative time (minutes)	0.035*	1.190(1.012–1.400)
Intra-operative Complications	1.000	–
Post-operative Complications	0.624	0.446(0.018–11.216)
Smoking	0.747	1.465(0.144 – 14.947)
Diabetes duration	0.112	6.600(0.646 – 67.434)
Presence of diabetes	0.410	2.647(0.261 – 26.823)

OR: Odd`s ratio C.I: Confidence interval
* Significant P-value < 0.05

5. Conclusion

Controlled diabetic patients should have the same chance of penile implant insertion to treat their ED as non-diabetic patients. Every effort should be made to shorten the operative time as it is crucial in reducing post-implant infection.

6. Author contributions

HAA: protocol development, data collection, and data analysis. AGZ: data analysis, manuscript writing and editing. TAG: data collection and manuscript editing. MAE: data analysis and manuscript editing. MMR: protocol development, supervision and manuscript editing. All authors read and approved the final manuscript.

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