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Comparison of the Effects of Testosterone on Pre- and Post-Hysterectomy Findings in Transgender Individuals

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ABSTRACT

Objective: **This study aimed to investigate the effect of testosterone on complications and blood parameters in transgender individuals undergoing hysterectomy.**

Methods: **This case-control study was carried out by examining the files and records in the hospital automation system of individuals who underwent laparoscopic hysterectomy and oophorectomy for a female to male transgender change in our hospital. To achieve normal male physiologic testosterone levels, transgender individuals (n = 12) were given intramuscular testosterone esters for two years before surgery. The drug dose was initially administered every three weeks, then adjusted according to the patients response. The control group (n=20) was selected from women who underwent hysterectomy and oophorectomy in the same hospital and study period.**

Results: **When the research and control groups were compared concerning blood values, there was no significant difference in preoperative white blood cell ($Z = 0.262$, $p = 0.795$), neutrophil ($Z = 0.384$, $p = 0.704$), and lymphocyte levels ($Z = 0.481$, $p = 0.634$). However, a significant difference was found in the postoperative levels of the same measurements ($Z = 2.457$, $p = 0.020$; $Z = 7.310$, $p = < 0.001$; and $Z = 6.586$, $p < 0.001$, respectively). Regarding preoperative and postoperative measurements, leukocyte and neutrophil levels increased, while lymphocyte and hemoglobin levels decreased in both groups ($p < 0.001$). Besides, the study group had higher creatinine levels than the control group ($Z = 3.817$, $p = 0.001$).**

Conclusion: **Testosterone has anti-inflammatory effects. Additionally, it substantially influences hemoglobin. Thus, testosterone can be considered as an option in selected cases. However, it's potentially harmful effect on the kidneys should always be kept in mind.**

KEY WORDS

transgenders, testosterone, white blood cell count, creatinine

INTRODUCTION

Background/rationale

Testosterone regulates secondary male sex characteristics, such as deepening of the voice, growth of male-pattern hair, and skeletal muscle growth[1)]. Additionally, it causes an increase in erythrocyte and hemoglobin (HB) due to its direct effect on the bone marrow and promotes the secretion of erythropoietin from the kidneys[2)].

Androgens are immunosuppressants that target many arms of the immune system and act to reduce the immune response, but the underlying mechanisms remain unidentified[3)]. It has been reported that decreased testosterone levels in men cause an increase in inflammatory markers[4)]. Furthermore, it has also been stated that low testosterone levels are common in patients with chronic inflammatory conditions, and acute withdrawal of testosterone promotes inflammatory response[5)].

Leukocytes make up about 7% of whole blood cells and are recognized as a reliable biomarker of inflammation[6)]. It is now known that white blood cells (WBC) offer numerous immunoregulatory phenotypes with anti-inflammatory functions[7)]. Therefore, it should also be remembered that leukocytes may increase with a normal reaction to wound healing and infection[8)].

The World Professional Association of Transgender Health recommends that individuals in transition receive hormone therapy for 12 months before gender-affirming hysterectomy[9)]. Hence, transgender people may be good candidates to investigate the effects of testosterone.

Objective

This study aimed to investigate the effects of testosterone on complications and blood parameters in transgender individuals who underwent laparoscopic hysterectomy and oophorectomy.

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MATERIALS AND METHODS

Study design

This case-control study was carried out by examining the files and records in the hospital automation system of individuals who underwent laparoscopic hysterectomy and oophorectomy for a female to male transgender. Ethical approval was obtained.

Per the protocol of the study hospital, hormone therapy of transgenders was adjusted for the normal male physiological range (300-1000 ng/dl)[10]. To achieve this target range, transgender individuals were given intramuscular injections (Sustanon 250 mg ampoule) containing testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg during the two years before surgery. The drug dose was initially administered every three weeks, then adjusted according to the patients response.

Participants

All transgenders who were admitted to the hospital during the study period were included in the research. The control group was selected from women who underwent hysterectomy and oophorectomy in the same hospital due to uterine myoma, adenomyosis, prolapsed uterus during the study period. Women with additional diseases, such as diabetes mellitus, hypertension, thyroid disease, rheumatic disease, malignancy, and cervical intraepithelial neoplasia 3, or those taking medications were excluded (Figure 1).

Variables

Preoperative blood samples were taken at 9:00 am the day before the surgery. On the other hand, postoperative blood samples were obtained eight hours after surgery.

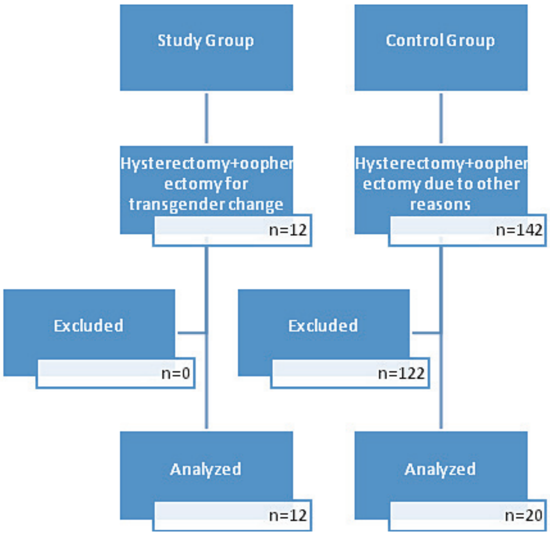

Figure 1: Participant flow diagram

The primary outcome variable of the study was the "postoperative WBC counts (10^3/µl). Other study variables were age, preoperative HB levels (g/dl), postoperative HB levels (g/dl), preoperative WBC counts (10^3/µl), preoperative neutrophil (NEU) counts (10^3/µl), postoperative NEU counts (10^3/µl), preoperative lymphocyte (LYM) levels (10^3/µl), postoperative LYM levels (10^3/µl), thyroid stimulation hormone (TSH)

Table 1: Comparison of the variables between study and control groups

	Group	n	Mean	SD	t	p
Age	Controls	20	51.20	7.05	9.954	**< 0.001**
	Cases	12	26.75	6.14		
Preoperative HB (g/dl)	Controls	20	12.46	1.86	5.249	**< 0.001**
	Cases	12	15.23	1.13		
Postoperative HB (g/dl)	Controls	20	10.68	1.68	5.034	**< 0.001**
	Cases	12	13.55	1.34		
Preoperative WBC (10^3/µL)	Controls	20	6.67	2.14	0.262	0.795
	Cases	12	6.86	1.80		
Postoperative WBC (10^3/µL)	Controls	20	10.37	3.48	2.457	**0.020**
	Cases	12	13.71	4.12		
Preoperative NEU (10^3/µL)	Controls	20	57.95	9.78	0.384	0.704
	Cases	12	59.16	6.25		
Postoperative NEU (10^3/µL)	Controls	20	72.69	7.70	7.310	**< 0.001**
	Cases	12	88.13	4.24		
Preoperative LYM (10^3/µL)	Controls	20	31.79	8.81	0.481	0.634
	Cases	12	30.31	7.74		
Postoperative LYM (10^3/µL)	Controls	20	17.76	6.55	6.586	**< 0.001**
	Cases	12	6.92	2.60		
TSH (mL)	Controls	20	2.72	1.48	1.283	0.209
	Cases	12	2.12	0.91		
Albumin (g/dl)	Controls	20	4.29	0.19	0.023	0.982
	Cases	12	4.29	0.22		
Urea (mg/dl)	Controls	20	22.75	8.94	0.838	0.409
	Cases	12	25.25	6.64		
Creatinine (mg/dl)	Controls	20	0.70	0.08	3.817	**0.001**
	Cases	12	0.84	0.14		

SD: Standard deviation, t: Independent samples t-test value, HB: Hemoglobin, WBC: White blood cells, NEU: Neutrophil, LYM: Lymphocyte, TSH: Thyroid stimulation hormone.

Table 2: Comparison of preoperative and postoperative blood parameters

Group	Variable	Mean	SD	t	p
Controls	Preoperative HB (g/dl)	12.46	1.86	8.388	**< 0.001**
	Postoperative HB (g/dl)	10.68	1.68		
	Preoperative WBC ($10^3/\mu L$)	6.67	2.14	6.494	**< 0.001**
	Postoperative WBC ($10^3/\mu L$)	10.37	3.48		
	Preoperative NEU ($10^3/\mu L$)	57.95	9.78	7.785	**< 0.001**
	Postoperative NEU ($10^3/\mu L$)	72.69	7.70		
	Preoperative LYM ($10^3/\mu L$)	31.79	8.81	8.358	**< 0.001**
	Postoperative LYM ($10^3/\mu L$)	17.76	6.55		
Cases	Preoperative HB (g/dl)	15.23	1.13	8.295	**< 0.001**
	Postoperative HB (g/dl)	13.55	1.34		
	Preoperative WBC ($10^3/\mu L$)	6.86	1.80	8.143	**< 0.001**
	Postoperative WBC ($10^3/\mu L$)	13.71	4.12		
	Preoperative NEU ($10^3/\mu L$)	59.16	6.25	13.919	**< 0.001**
	Postoperative NEU ($10^3/\mu L$)	88.13	4.24		
	Preoperative LYM ($10^3/\mu L$)	30.31	7.74	10.528	**< 0.001**
	Postoperative LYM ($10^3/\mu L$)	6.92	2.60		

SD: Standard deviation, t: Paired samples t-test value, HB: Hemoglobin, WBC: White blood cells, NEU: Neutrophil, LYM: Lymphocyte, TSH: Thyroid stimulation hormone.

levels (ml), albumin levels (g/dl), urea levels (mg/dl), creatinine levels (mg/dl), presence of complications (yes/no), wound site infection (yes/no), and smoking status (yes/no).

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS for Windows, Version 25.0, Chicago, IL, USA) program. Numerical variables were presented as means and standard deviations, while categorical data were given as frequencies and percentages. The fitting of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Parametric variables were compared using the independent samples t-test and paired sample t-test. Besides, Chi-square or Fisher's exact test was used as appropriate to compare categorical variables. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS AND THEIR DISCUSSION

When the study and control groups were compared concerning blood values, there was no significant difference in preoperative WBC counts (Z = 0.262, p = 0.795), NEU counts (Z = 0.384, p = 0.704), and LYM levels (Z = 0.481, p = 0.634). However, a significant difference was found in the postoperative period (Z = 2.457, p = 0.020; Z = 7.310, p = < 0.001; and Z = 6.586, p < 0.001, respectively) (Table 1). Because

Table 3: Comparison of groups regarding complications and smoking status

		Group			
		Controls	Cases	χ^2	p
Complications	No	17	12	1.986	0.274*
	Yes	3	0		
Wound infection	No	18	12	1.280	0.516*
	Yes	2	0		
Smoking	No	15	9	0.000	1.000
	Yes	5	3		

χ^2: Chi-square test, *Fisher's-Exact test

age was significantly different between the groups, all analyses were repeated after weighting by age, which revealed no change in the significance levels.

There were significant changes in all blood parameters of both the study and control groups regarding preoperative and postoperative measurements. On the other hand, leukocyte and neutrophil levels increased, while lymphocyte and hemoglobin levels decreased (Table 2).

There were no significant differences between the groups concerning complications and smoking status (Table 3).

Key results

Transgenders using testosterone for the last two years had higher hemoglobin levels than cisgender women, both preoperatively and postoperatively. Furthermore, levels of WBC, NEU, and LYM between groups were similar before surgery but different after surgery. Both groups had higher WBC and NEU counts and lower LYM levels in postoperative measurements compared to preoperative values. However, this change was more striking in the transgender group. Another difference between groups was in the creatinine (transgenders had higher creatinine levels).

Limitations

Some limitations of this study deserve mentioning. The absence of other inflammatory markers, such as c-reactive protein (CRP) and homocysteine, can be considered as a limitation. Also, it would be more effective if the long-term consequences of the inflammation were recorded. Unfortunately, not all participants who were discharged returned to the hospital after surgery. Therefore, the records of the participants for long-term follow-up were not available.

Interpretation

It has been reported that hemoglobin levels are affected by testosterone concentration[11)]. For instance, hemoglobin levels can be regulated by testosterone, and low testosterone concentrations may have been associated with anemia. Additionally, testosterone is able to increase hemoglobin in patients with unexplained anemia[12)]. In this study, in line with previous research, testosterone was demonstrated a significant effect on hemoglobin concentrations. Hemoglobin was significantly higher in the group receiving testosterone in both pre- and postoperative periods.

WBC count is a nonspecific indicator, which increases in infection, inflammation, stress, tissue necrosis, or hemorrhage. Additionally, even a relationship between wound severity and early leukocytosis has been reported. Besides, it has been stated that surgery, which is a kind of trauma or controlled wound, causes an increase in neutrophil and monocyte counts with lymphocytopenia[13)].

It is common to find leukocytosis in the first postoperative day after various surgical interventions. This situation may not be due to postoperative infectious complications, invasiveness of the surgery, or the use of anesthesia, but may be related to the response to psychological or physiological stress, transient bacteremia, or bleeding[14)].

The findings of this study are in line with previous research. Changes in blood parameters of both groups occurred, as stated before. However, these effects were more dramatic in people using testosterone.

Former studies have shown that the use of the steroid dexamethasone in the perioperative period is strongly associated with postoperative leukocytosis[13)]. Besides, it was reported that glucocorticoids, which have extensive anti-inflammatory effects, increase the number of neutrophils. Furthermore, these hormones decrease the absolute numbers of lymphocytes[14].

The findings of testosterone in this study coincide with dexamethasone outcomes. For this reason, testosterone can be considered to have anti-inflammatory properties. However, the opinion to use testosterone as an anti-inflammatory agent in selected cases should be supported by further studies. As a matter of fact, it has been shown that testosterone replacement therapy in Klinefelter's syndrome reduces the levels of serum antibodies, cytokines, T-cells, and B-cells. The immunosuppressive role of testosterone has been more clearly demonstrated in avian model studies[15].

Another essential point is the absence of any difference between trans- and cisgenders regarding the presence of complications and wound site infection. It should be emphasized that there were no complications or wound infections in the transgenders' group. Perhaps, this is due to the low number of participants. Thus, since the difference between the groups did not reach a statistical significance, larger studies may reveal a possible effect.

Because the majority of individuals affected by autoimmune diseases are women, much emphasis has been placed on the role of female sex hormones and the effect of these hormones on different immune cell subsets . In support of this view, estrogen has been reported to play a role in the regulation of the autoimmune response[16].

There is another interesting point uncovered by this study. While before surgery, there was no difference between the groups, except for hemoglobin, after surgery, the difference became prominent in WBC, HB, and LYM levels. This may be due to the fact that transgender individuals still had ovaries before operations, and the hormones released from the ovaries may have limited the effects of testosterone. As mentioned before, estrogen also has an immunomodulatory effect.

Testosterone has been reported to directly modulate renal perfusion[17]. It was also claimed that testosterone can make a significant contribution to the gender differences observed in the progression of chronic kidney disease and the development of acute kidney injury. Hence, in this study, it was evaluated that the creatinine elevation observed in transgender individuals may be due to the effects of testosterone.

CONCLUSION

Transgender individuals are suitable candidates to assess the short- and long-term effects of testosterone. This group can serve as candidates to conduct detailed investigations in this area, including medical applications, in an ethically acceptable manner. Testosterone has anti-inflammatory effects. Additionally, it substantially influences hemoglobin. Thus, testosterone can be considered as an option in selected cases. However, it's potentially harmful effect on the kidneys should always be kept in mind.

CONFLICT OF INTEREST

The author have no conflict of interest in this study.

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