Zeynep Kamil Med J 2022;53(2):68–74
DOI: 10.14744/zkmj.2022.48802

ORIGINAL ARTICLE

Semen analysis results are negatively affected in patients with vitiligo: A cross-sectional study from Turkey

[1]Müstecep KAVRUT
[2]Nur DOKUZEYLÜL GÜNGÖR
[3]Arzu YURCİ
[4]Kağan GÜNGÖR
[5]Kaan ÇİL

[1]Private Office, İstanbul, Turkey

[2]Department of Obstetrics and Gynecology, Bahçeşehir University Faculty of Medicine, İstanbul, Turkey

[3]IVF Unit, Memorial Hospital, Kayseri, Turkey

[4]Department of Endocrinology and Metabolism, Medeniyet University Faculty of Medicine, İstanbul, Turkey

[5]Medical Faculty, Otto von Guericke University, Magdeburg, Germany

ORCID ID
MK : 0000-0001-7049-0461
NDG : 0000-0002-7234-3876
AY : 0000-0003-4808-9019
KG : 0000-0003-1019-3769
KÇ : 0000-0001-7667-6232

ABSTRACT

Objective: Male fertility can be affected by a variety of organ diseases, commonly including the testis, in the form of cryptorchidism and hypogonadism. The evidence related to the fact that male infertility depends on skin disease is still not adequate. The aim of the study was to evaluate the clinical features and semen analysis results of vitiligo patients and control cases.

Material and Methods: This cross-sectional study was conducted between January 2015 and January 2021 by retrospectively evaluating patients who underwent sperm analysis at İstanbul Medeniyet University Göztepe Training and Research Hospital. Patients with vitiligo (n=76) were included in the study as the vitiligo group. The control group was selected from age- and body mass index-matched patients who underwent semen analysis (n=71).

Results: The mean age was 30.29±4.18 years, the mean age at onset of vitiligo was 23.66±3.96 years, and the mean disease duration was 6.36±2.80 years in the vitiligo group. The free T4 (FT4) levels were significantly lower in the vitiligo group than in the control group ($p<0.001$). When we evaluated semen analysis results, we found sperm concentration ($p<0.001$), A + B motility ($p<0.01$), and morphology ($p<0.001$) significantly better in the controls than in the patients with vitiligo.

Conclusion: We found that the FT4 level was lower, and semen analysis results were negatively affected in patients with vitiligo. The clinical management of vitiligo should also include its effects on the semen and the male reproductive system.

Keywords: Male infertility, semen analysis, vitiligo.

Cite this article as: Kavrut M, Dokuzeylül Güngör N, Yurci A, Güngör K, Çil K. Semen analysis results are negatively affected in patients with vitiligo: A cross-sectional study from Turkey. Zeynep Kamil Med J 2022;53(2):68–74.

Received: March 06, 2022 **Accepted:** March 22, 2022 **Online:** May 23, 2022
Correspondence: Nur DOKUZEYLÜL GÜNGÖR, MD. Bahçeşehir Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Kliniği, Muğla, Turkey.
Tel: +90 532 383 49 65 **e-mail:** drnur9eylul@hotmail.com
Zeynep Kamil Medical Journal published by Kare Publishing. Zeynep Kamil Tıp Dergisi, Kare Yayıncılık tarafından basılmıştır.

INTRODUCTION

Vitiligo is a multifactorial disorder characterized by the loss of functional melanocytes, and both genetic and nongenetic factors play a pathogenic role.[1] The precise cause of vitiligo is unknown. The worldwide prevalence of vitiligo is 0.2%–1.8%.[2] It is believed that there is a progressive decrease in functional melanocytes. Autoimmune mechanisms, cytotoxic mechanisms, intrinsic melanocyte defects, oxidant–antioxidant mechanisms, and neural mechanisms are among the most popular theories in the development of vitiligo.[3] Recent data provide strong evidence supporting the autoimmune pathogenesis of vitiligo. Asymptomatic depigmented patches and macules are the most common presentation of vitiligo, which can be classified as segmental and nonsegmental. Although it is not a life-threatening disease, it decreases the quality of life in the affected person.[4] Male infertility is also a common problem, contributing to almost 50% of all infertility problems.[5] It is almost always defined by abnormal findings in semen analysis, which gives information about semen volume, sperm concentration, motility, and morphology. Both seminal leukocytes and sperm cells generate reactive oxygen species (ROS) and can interfere with sperm function by peroxidation of sperm lipid membranes and the creation of toxic fatty acid peroxides. ROS also have a normal physiologic role in the capacitation and the acrosome reaction. Elevated ROS have been implicated as a cause of male infertility.[5,6] Male fertility can be affected by a variety of organ diseases, commonly including the testis, in the form of cryptorchidism and hypogonadism.[7] Although the prevalence of skin diseases is not common, the associated male infertility represents a challenge due to the difficulty of its management.[7]

The aim of this study was to compare the clinical features and semen analysis results of vitiligo and control cases.

MATERIAL AND METHODS

This cross-sectional study was conducted between January 2015 and January 2021 by retrospectively evaluating patients who underwent sperm analysis at İstanbul Medeniyet University Göztepe Training and Research Hospital. The study was approved by the medical ethics committee of İstanbul Medeniyet University Göztepe Training and Research Hospital (No: 2021/0008) and by the Local Institutional Review Board, and it was conducted according to the Helsinki Declaration.

Patients

All patients aged between 25 and 45 years who underwent semen analysis at the relevant dates were evaluated in terms of the study (n=5167). Subjects with the additional disease were excluded from the study (malignancy, autoimmune disorders, diabetes mellitus, hypothyroidism, and hyperthyroidism). Patients with vitiligo (n=76) were included in the vitiligo group. The diagnosis of vitiligo was made clinically and using Wood's lamp. None of the men with vitiligo had chromosomal abnormalities or varicoceles. In 2011, an international consensus classified vitiligo into two major forms: nonsegmental vitiligo (NSV) and segmental vitiligo (SV).[8] We also divided the patients with vitiligo into two groups as NSV and SV. We divided patients with vitiligo into three groups according to their sperm concentrations as follows: patients with vitiligo + normal semen analysis as group A, patients with vitiligo+oligozoospermia (sperm concentration between 5 and 15×10^6 mL^{-1}) as group B, and patients with vitiligo + severe oligozoospermia (sperm concentration $<5\times10^6$ /mL) as group C. The control group (n=71) was selected from among patients who underwent semen analysis and were matched according to age and body mass index (BMI) to the patients with vitiligo. The flow chart of the study is shown in Figure 1.

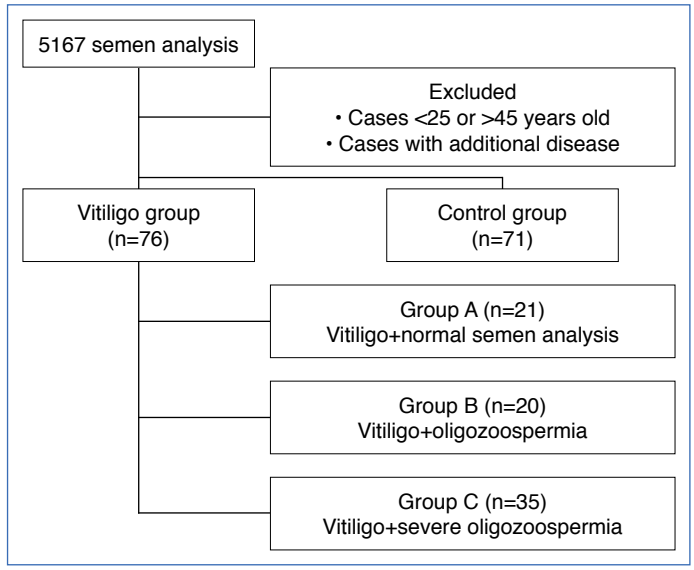

Figure 1: Flow diagram of the study.

Measurements

The parameters examined in the study were as follows: characteristics of cases (age, BMI, and family history); disease features (duration of disease, clinical type, Koebner phenomenon, and halo nevus); and the level of hormones [follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroxine (FT4), thyroid-stimulating hormone (TSH), testosterone, prolactin]. Blood glucose; semen analysis (volume, sperm concentration, total motility, A + B motility, and morphology); age; age of onset; clinical type; and family history were recorded. Routine biochemical tests under fasting conditions were conducted.

Statistical Analysis

All analyses were performed using the SPSS v21 statistical package (SPSS, Inc., Chicago, IL, USA). For the normality check, histogram and Q–Q plots were used. The data are given as mean±standard deviation or median (minimum–maximum) for continuous variables according to the normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed using the independent samples t-test or one-way analysis of variances depending on the count of the groups. Pairwise comparisons of these variables were performed using Tukey's test or Tamhane's test depending on the homogeneity of variances. Nonnormally distributed variables were analyzed using the Mann–Whitney U test or the Kruskal–Wallis test depending on the count of the groups. Pairwise comparisons of these variables were performed using the Bonferroni correction. Categorical variables were analyzed using the Chi-squared test. $p<0.05$ was accepted as statistically significant.

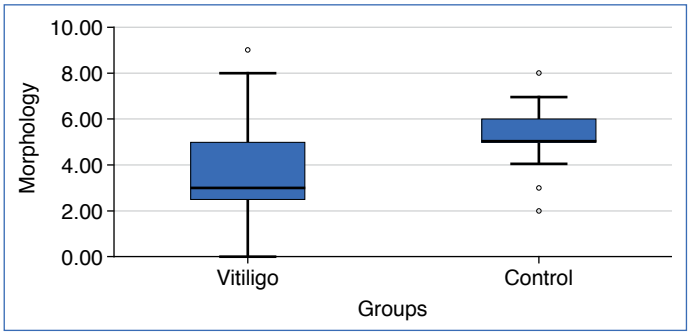

Figure 2: Boxplot of the morphology for the vitiligo and control groups.

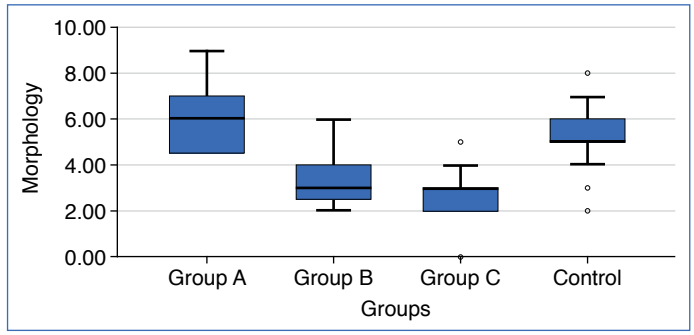

Figure 3: Boxplot of the morphology for all groups.

RESULTS

Seventy-six patients with vitiligo and 71 healthy controls were included in our study. The mean age was 30.29±4.18 (range 25–45) years. The mean age at onset was 23.66±3.96 (range 15–35) years, and the mean duration of disease was 6.36±2.80 (range 2–20) years in the vitiligo group. Sixty-seven (88.16%) patients had NSV and 9 (11.84%) had SV. Seven (9.21%) patients had a family history, 3 (3.95%) had the Koebner phenomenon, and 1 (1.32%) patient had halo nevus. Free T4 (FT4) levels were significantly lower in the vitiligo group than in the control group ($p<0.001$). There were no significant differences between the groups regarding age, BMI, FSH, LH, TSH, testosterone, prolactin, and blood glucose levels. When we evaluated the semen analysis results, we found that sperm concentration, A + B motility, and morphology were significantly higher in the controls than in the patients with vitiligo ($p<0.001$, $p<0.01$, and $p<0.001$) (Fig. 2).

There were no significant differences between the groups concerning volume and total motility (Table 1). We divided patients with vitiligo into three groups according to their sperm concentrations. There were no significant differences between groups regarding age, age at onset, duration of disease, BMI, clinical type, family history, Koebner phenomenon, and halo nevus. FT4 levels were significantly higher in the control group than in the other groups ($p<0.001$). There were no significant differences between group A, group B, and group C concerning FT4 levels. In addition, we found no significant differences between the four groups with regard to FSH, LH, TSH, testosterone, prolactin, and blood glucose levels.

We found no significant differences between the four groups with regard to semen volume. Sperm concentration was significantly higher in group A and the control group than in group B and group C. In addition, sperm concentrations were significantly higher in group B than in group C ($p<0.001$). Total motility was significantly higher in group A than in the other groups and significantly higher in the control group than in group B and group C ($p<0.001$). A + B motility was significantly higher in group A and the control group than in group B and group C. In addition, A + B motility was significantly higher in group B than in group C ($p<0.001$). Morphology was significantly higher in group A and the control group than in group B and group C ($p<0.001$) (Fig. 3). A summary of the variables and analysis results according to the group is shown in Table 2.

DISCUSSION

Vitiligo can affect different aspects of patients' lives, especially their external appearance. In this study, in which clinical features and semen analysis results were evaluated in patients with vitiligo, the FT4 value was lower in patients with vitiligo compared with the control group. Also, sperm concentration, A + B motility, and morphology were statistically significantly lower in the vitiligo group.

Skin disorders can be associated with other diseases. In a recent meta-analysis, Yuan et al.[9] examined the association of thyroid disorders with vitiligo, showing that various thyroid dysfunctions, especially subclinical hypothyroidism, were associated with vitiligo. In different studies, it has been shown that thyroid hormone levels are significantly different in patients with vitiligo when compared with healthy individuals.[10] In accordance with the literature, in our study, a significant difference was found in thyroid hormone levels (FT4) between the vitiligo and control groups. It will be useful to follow up with patients with vitiligo regularly in terms of thyroid diseases. In addition, it has been shown that the change in thyroid hormone levels negatively affects semen analysis parameters. Increased thyroid hormone levels can negatively affect semen volume, motility, and morphology.[11,12] The difference in FT4 levels among the groups identified in our study may also be a confounding factor affecting the semen analysis results. Inflammation and oxidative stress may affect sperm quality.[13,14]

In an experimental animal study, Umaoka et al.[15] reported that skin-derived cytokines triggered in diseases with inflammation in the skin negatively affect spermatogenesis and sperm viability. Azenabor et al.[16] reported that increased cytokine and oxidative stress levels in diseases that caused inflammation negatively affected sperm health and might cause DNA damage and apoptosis. They emphasized that the increase in inflammation in the body might be indirectly related to male infertility due to the decrease in sperm quality. Although vitiligo is a common skin disorder, the pathogenesis remains unknown. It was shown that inflammation and oxidative stress was accepted as a trigger factor in melanocyte degeneration. Free radicals can harm protein, carbohydrate, lipid, and DNA.[17–19]

Considering the results of these studies, we thought that one of the reasons for the more negative results in sperm analysis parameters in patients with vitiligo in our study might be due to increased inflammation level. In vitiligo, the autoimmunity hypothesis is primarily focused on genetic factors and the relationship of vitiligo with other autoimmune disorders. It is also supported by the high prevalence of organ-specific autoantibodies in patients with vitiligo compared

Table 1: Summary of the variables and analysis results according to the groups

	Groups		
	Vitiligo (n=76)	Control (n=71)	p
Age	30 (25–45)	30 (25–40)	0.878
Age at onset	23.66±3.96	–	N/A
Duration of disease	6 (2–20)	–	N/A
Body mass index	24.58±2.28	24.39±1.49	0.565
Clinical type			
Nonsegmental	67 (88.16%)	–	N/A
Segmental	9 (11.84%)	–	
Family history	7 (9.21%)	–	N/A
Koebner phenomenon	3 (3.95%)	–	N/A
Halo nevus	1 (1.32%)	–	N/A
FSH	4.73±1.22	4.75±1.22	0.911
LH	4.48±1.28	4.64±1.21	0.448
FT4	1.10 (0.90–1.41)	1.20 (1.01–1.41)	**<0.001**
TSH	2.00 (1.50–4.00)	2.18 (1.58–3.56)	0.555
Testosterone	4.23 (3.11–7.28)	4.50 (2.44–7.28)	0.064
Prolactin	14.5 (10–20)	14.80 (4.23–19.67)	0.854
Blood glucose	86.53±4.67	86.13±4.98	0.616
Semen analysis			
Volume	3.43±0.94	3.46±0.81	0.799
Sperm concentration	9 (0.5–112)	45 (16–111)	**<0.001**
Total motility	57.97±14.81	61.30±9.26	0.103
A + B motility	29.95±9.21	39.79±7.93	**<0.001**
Morphology	3 (0–9)	5 (2–8)	**<0.001**

Data are given as mean±standard deviation or median (minimum–maximum) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; FT4: Thyroxine; TSH: Thyroid-stimulating hormone; N/A: Non-applicable.

with the normal population. The destruction of melanocytes and the appearance of antibodies against them are key points in the autoimmune theory.[20] It is now evident that vitiligo is an autoimmune disease, implicating a complex relationship between programming and function of the immune system, aspects of the melanocyte autoimmune target, and dysregulation of the immune response.[21] Oxidative stress may be the trigger factor in the destruction of melanocytes.[22] Skin diseases may affect male fertility at pretesticular (hypothalamic/pituitary), testicular, and posttesticular (genitourinary ducts/accessory sex organs) levels. In general, it has been shown that many severe illnesses depress testicular function, as evidenced by low testosterone levels, unchanged immunoreactive inhibin levels, and decreased or mildly increased gonadotropin levels.[7] This kind of transient and reversible biochemical androgen deficiency (secondary hypogonadism) is very common, and it is considered a normal response. In addition, severe skin disorders with a high Charlson Comorbidity Index showed a significantly higher rate of semen abnormalities, such as low semen volume, sperm count, motility, and increased abnormal forms.[23] On the other hand, and because the skin and its appendages are androgen-dependent, male infertility due to hypogonadism can be associated with secondary skin changes. Several genetically determined skin disorders may be associated with hypogonadism. Expectedly, affected patients have both cutaneous and extracutaneous manifestations including involvement of the male reproductive system. Except for polyarteritis nodosa and erythema nodosum leprosum, testicular involvement in autoimmune diseases is unusual. Nevertheless, there are few reports about the affection of male fertility in a variety of other autoimmune diseases.[7] Due to this tendency to other autoimmune disorders, there can also be an immune response and antibody formation in the testis against itself in patients with vitiligo. It is very difficult to evaluate the association of uncommon diseases. The association between vitiligo and male infertility can also be evaluated

Table 2: Summary of the variables and analysis results according to the groups

	Groups				
	Group A (n=21)	Group B (n=20)	Group C (n=35)	Control (n=71)	p
Age	30.5 (27–45)	27.5 (25–36)	31 (25–39)	30 (25–40)	0.372
Age at onset	23.14±3.65	22.35±3.96	24.71±3.95	–	0.079
Duration of disease	5.5 (5–20)	6 (4–10)	6 (2–14)	–	0.432
Body mass index	25.10±3.02	24.35±1.20	24.39±2.25	24.39±1.49	0.492
Clinical type					
Nonsegmental	17 (80.95%)	20 (100.00%)	30 (85.71%)	–	0.140
Segmental	4 (19.05%)	0 (0.00%)	5 (14.29%)	–	
Family history	0 (0.00%)	1 (5.00%)	6 (17.14%)	–	0.075
Koebner phenomenon	0 (0.00%)	0 (0.00%)	3 (8.57%)	–	0.161
Halo nevus	0 (0.00%)	0 (0.00%)	1 (2.86%)	–	0.552
Semen analysis					
Volume	3.40±1.00	3.45±0.97	3.43±0.92	3.46±0.81	0.993
Sperm concentration	39 (18–112)[a]	11 (8–14)[b]	3.21 (0.5–4.8)[c]	45 (16–111)[a]	**<0.001**
Total motility	78.43±8.13[a]	51.75±5.06[c]	49.26±8.44[c]	61.30±9.26[b]	**<0.001**
A + B motility	41.62±4.47[a]	28.90±2.15[b]	23.54±6.78[c]	39.79±7.93[a]	**<0.001**
Morphology	6 (5–9)[a]	3 (2–6)[b]	3 (0–5)[b]	5 (2–8)[a]	**<0.001**

Data are given as mean±standard deviation or median (minimum–maximum) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Same letters denote the lack of statistically significant differences between groups.

in this context. Abdel-Naser and Zouboulis underlined that the association of male infertility with skin diseases could be seen in various congenital syndromes, as well as in acquired skin diseases, and that the medication for skin diseases might also cause male infertility.[7] Although the current drugs used by the patients were not evaluated in our study, it was thought that the drugs used for vitiligo might also have affected sperm parameters. In many syndromes, there is an association of skin pigmentation disorders with male infertility (hypogonadism and cryptorchidism).[24,25] As suggested in our study, it has been shown that there may be a relationship between hypopigmented lesions and male infertility in various syndromes such as McCune–Albright, Prader–Willi, Pallister–Killian, and Fanconi anemia.[26–28] To the best of our knowledge, this study is the first to investigate the relationship between vitiligo and sperm analysis differences. Although the mechanism could not be demonstrated in studies evaluating the relationship between hypopigmented areas and sperm parameters, knowing this relationship and acting in that direction will facilitate early treatments. Although the underlying pathogenesis of vitiligo has not been revealed, various theories have been proposed on this issue. In different studies, zinc-α2-Glycoprotein (ZAG), a protein that is thought to have a role in the relationship between vitiligo and male infertility, has been mentioned.[29,30] This protein is secreted in various fluids in the body and has many functions. The ZAG protein is involved in the regulation of melanin synthesis.[31] ZAG is also an important protein in terms of lipolysis and lipid metabolism and is associated with obesity.[32,33] It has been suggested that lipid metabolism is an important factor in the regulation of sperm movements, and sperm motility may be affected by disrupting this metabolism in ZAG protein problems.[34,35] In addition, the ZAG protein can directly affect sperm motility through membrane activation.[35] In different studies, it has been shown that the ZAG protein is associated with the adequacy of sperm motility during the fertilization process.[36] For these reasons, we thought that disorders of the ZAG protein, which were suggested to have a role in both vitiligo pathogenesis and sperm motility, could account for the results of our study.

Limitations

This study has several limitations. The retrospective design of the study is an important limitation. Although the relationship between vitiligo and sperm parameters has been examined, the direction and cause of this relationship could not be determined due to the study design. The sample of the study consists of patients who gave semen samples for various reasons. The indication for semen analysis was not examined in our study. In cases with an indication for semen analysis, the possibility of finding an abnormality in the results may be higher. Therefore, selection bias may have occurred in the determination of the groups, and our control group cannot be considered completely healthy. Another limitation is that the FT4 value, which is a variable that may affect the semen analysis results, is different between the groups. FT4 may have been a confounding factor affecting semen analysis results.

CONCLUSION

We found that FT4 levels were lower and semen analysis results (sperm concentration, A + B motility, and morphology) were more negatively affected in patients with vitiligo. The clinical management of vitiligo should also include its effects on the skin and male reproductive system. Comprehensive studies examining the relationship between vitiligo and male infertility are valuable in reinforcing the results of our study.

Statement

Ethics Committee Approval: The İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 27.01.2021, number: 2021/0008).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NDG; Design – MK, KG; Supervision – KÇ, AY; Resource – KG, AY; Materials – KG, NDG, MK; Data Collection and/or Processing – NGD, MK,AY; Analysis and/or Interpretation – KÇ, MK; Literature Search – KÇ; Writing – NDG, MK; Critical Reviews – NDG, MK.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE; Vitiligo Working Group. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol 2017;77:1–13.
2. Zhang Y, Cai Y, Shi M, Jiang S, Cui S, Wu Y, et al. The prevalence of Vitiligo: A meta-analysis. PLoS One 2016;11:e0163806.
3. Halder RM, Chappell JL. Vitiligo update. Semin Cutan Med Surg 2009;28:86–92.
4. Bergqvist C, Ezzedine K. Vitiligo: A review. Dermatology 2020;236:571–92.
5. Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol 2015;13:37.
6. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci 2015;8:191–6.
7. Abdel-Naser MB, Zouboulis CC. Male fertility and skin diseases. Rev Endocr Metab Disord 2016;17:353–65.
8. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CC, et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012;25:E1–13.
9. Yuan J, Sun C, Jiang S, Lu Y, Zhang Y, Gao XH, et al. The prevalence of thyroid disorders in patients with vitiligo: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2019;9:803.
10. Mubki T, Alissa A, Mulekar S, Albargawi S, Youssef M, Aljasser M. Association of vitiligo with anemia, vitamin B12 deficiency, diabetes mellitus, and thyroid dysfunction in Saudi Arab patients: A case control study. J Dermatol Dermatol Surg 2017;21:72–6.
11. Wajner SM, Wagner MS, Maia AL. Clinical implications of altered thyroid status in male testicular function. Arq Bras Endocrinol Metabol 2009;53:976–82.
12. La Vignera S, Vita R. Thyroid dysfunction and semen quality. Int J Immunopathol Pharmacol 2018;32:2058738418775241.
13. Bisht S, Faiq M, Tolahunase M, Dada R. Oxidative stress and male infertility. Nature Reviews Urology 2017;14:470–85.
14. Alahmar AT. Role of oxidative stress in male infertility: An updated review. J Hum Reprod Sci 2019;12:4–18.
15. Umaoka A, Takeuchi H, Mizutani K, Seo N, Matsushima Y, Habe K, et al. Skin inflammation and testicular function: Dermatitis causes male infertility via skin-derived cytokines. Biomedicines 2020;8:293.
16. Azenabor A, Ekun AO, Akinloye O. Impact of inflammation on male reproductive tract. J Reprod Infertil 2015;16:123–9.
17. Frisoli ML, Harris JE. Vitiligo: Mechanistic insights lead to novel treatments. J Allergy Clin Immunol 2017;140:654–62.
18. Solak B, Dikicier BS, Cosansu NC, Erdem T. Neutrophil to lymphocyte ratio in patients with vitiligo. Postepy Dermatol Alergol 2017;34:468–70.
19. Boniface K, Seneschal J, Picardo M, Taïeb A. Vitiligo: Focus on clinical aspects, ımmunopathogenesis, and therapy. Clin Rev Allergy Immunol 2018;54:52–67.
20. van den Wijngaard R, Wankowicz-Kalinska A, Pals S, Weening J, Das P. Autoimmune melanocyte destruction in vitiligo. Lab Invest 2001;81:1061–7.
21. Spritz RA, Andersen GH. Genetics of vitiligo. Dermatol Clin 2017;35:245–55.
22. Speeckaert R, Dugardin J, Lambert J, Lapeere H, Verhaeghe E, Speeckaert MM, et al. Critical appraisal of the oxidative stress pathway in vitiligo: A systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2018;32:1089–98.
23. Eisenberg ML, Li S, Behr B, Pera RR, Cullen MR. Relationship between semen production and medical comorbidity. Fertil Steril 2015;103:66–71.
24. Stratakis CA. Carney complex: A familial lentiginosis predisposing to a variety of tumors. Rev Endocr Metab Disord 2016;17:367–71.
25. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: Epidemiology and developments in disease management. Clin Epidemiol 2015;7:281–93.
26. de Kerviler E, Guermazi A, Zagdanski AM, Gluckman E, Frija J. The clinical and radiological features of Fanconi's anaemia. Clin Radiol 2000;55:340–5.
27. Verhagen MM, Abdo WF, Willemsen MA, Hogervorst FB, Smeets DF, Hiel JA, et al. Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology 2009;73:430–7.
28. Blyth M, Maloney V, Beal S, Collinson M, Huang S, Crolla J, et al. Pallister-Killian syndrome: A study of 22 British patients. J Med Genet 2015;52:454–64.
29. Bagherani N. The Newest hypothesis about Vitiligo: Most of the suggested pathogeneses of vitiligo can be attributed to lack of one factor, Zinc-α2-Glycoprotein. ISRN Dermatol 2012;2012:405268.
30. El-Rifaie AAAS, Gohary YM, Abd-El Aziz GM, Owies FO. Zinc-α2-Glycoprotein (ZAG): A new deficiency in vitiligo patients. Skinmed 2019;17:248–53.
31. Wei X, Liu X, Tan C, Mo L, Wang H, Peng X, et al. Correction to: Expression and function of Zinc-α2-Glycoprotein. Neurosci Bull 2019;35:778.
32. Severo JS, Morais JBS, Beserra JB, Dos Santos LR, de Sousa Melo SR, de Sousa GS, et al. Role of zinc in Zinc-α2-glycoprotein metabolism in obesity: A review of literature. Biol Trace Elem Res 2020;193:81–8.

33. Liu M, Zhu H, Dai Y, Pan H, Li N, Wang L, et al. Zinc-α2-Glycoprotein is associated with obesity in Chinese people and HFD-Induced obese mice. Front Physiol 2018;9:62.
34. Frenette G, Thabet M, Sullivan R. Polyol pathway in human epididymis and semen. J Androl 2006;27:233–9.
35. Hassan MI, Waheed A, Yadav S, Singh TP, Ahmad F. Zinc alpha 2-glycoprotein: A multidisciplinary protein. Mol Cancer Res 2008;6:892–906.
36. Ding Z, Qu F, Guo W, Ying X, Wu M, Zhang Y. Identification of sperm forward motility-related proteins in human seminal plasma. Mol Reprod Dev 2007;74:1124–31.