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Original Research

Investigation of gene expression and genetic simultaneous control associated with erectile dysfunction and diabetes

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Abstract: Diabetes can cause some diseases or abnormalities. One of the disorders caused by diabetes may be erectile dysfunction (ED). ED is sexual dysfunction characterized by the inability to establish or maintain an erect penis during sexual activity and is a common problem of men with chronic type 2 diabetes. These processes, disorders and diseases are highly influenced by the genetics of individuals. In this study, the relationship between genes and diabetes and ED has been explored by a system biology approach. For this purpose, the samples from ten control and diabetic-ED rats were collected. After a search in Gene Expression Omnibus (GEO), series with accession number GSE2457 comprising of 5 normal and 5 diabetic-ED rats were selected. Raw CEL files of these samples were normalized with robust multi-array average (RMA) expression measure method by using the linear models for microarray data (LIMMA) R package. The extracted probe IDs were transformed into 10451 unique and validated official gene symbols. Then, differentially expressed genes (DEGs) were identified between control and normal penile mucosa by employing the LIMMA R package. DEGs were classified by utilizing KEGG to underlying pathways by Enrichr. The expression values of DEGs were used to construct a gene regulatory network (GRN), by the GENEI3 R package. To analyze the topology of constructed GRNs, betweenness centrality was calculated. Genes with higher betweenness centrality scores were then identified, through the CytoNCA. We then took the commonality of DEGs genes and high-top ranking genes from CytoNCA via a predicted interaction network using GeneMANIA as the most likely important genes in erectile dysfunction. Among the 374 DEGs studied, 146 DEGs showed up-regulation and 228 DEGs displayed down-regulation expression in diabetic-ED rats. According to the Volcano plot, the dpp4, LOC102553868, Ndufa412, Oxct1, Atp2b3 and Zfp91 gene down-regulated and Lpl, Retsat, B4galt1 and Pdk4 genes up-regulated in ED and diabetic rats. Furthermore, genes like dpp4 acted as hubs in the inferred GRN.

Key words: Differentially expressed genes; Gene expression omnibus; rat; sexual dysfunction.

Introduction

Erectile dysfunction (ED) means the inability to create or maintain an adequate and sufficient erection to have a successful and satisfying sexual relationship, which is one of the most common sexual disorders in men. More than 150 million men worldwide are affected by the disorder, and it is projected that by 2025 this number will reach 322 million, double the current number. Therefore, considering the significant negative impact that this disorder has on the quality of life and marital and interpersonal relationships of people with the disease; there seems to be a need for more effort and study to prevent and treat this disorder (1).

In the past, there were only psychological causes for ED, but today, 15 to 72% of men under the age of 40 also have organic causes. These include vascular and neurological problems, Peyronie's disease, side effects of medications and endocrine disorders. Young men with MS, epilepsy or spinal cord trauma are also more likely to develop ED. Overall, 52% of men in their 40s and 70s have some degree of ED (2, 3).

According to a study conducted in Turkey on 948 men with an IIEF of less than 21, these individuals were examined using physical examination, NPT, and color-coded ultrasound of the penis and found that 14.8% of men under the age of 40 had ED. There are organic causes: MS in men under 40 years of age increases the

incidence of ED by 2.2 times and epilepsy by 1.8 times. Femoral fractures also increase the risk of ED in young men due to their effect on pudendal nerves (2).

Diabetes is a group of metabolic diseases in which blood sugar levels are elevated for a long time. It is one of the most common endocrine and metabolic diseases and is caused by environmental factors (3). With the development of society and economy, the change of lifestyle and the aging of the population, the incidence of diabetes is increasing year by year. So far, diabetes has become a threat to people's health and life following cardiovascular disease and cancer. Type 2 diabetes (T2D) is the main type of diabetes and is related to insulin resistance and β-cell dysfunction. Some studies have shown that systemic insulin resistance, mild inflammation, chronic hypercholesterolemia, and excessive metabolic fuel can cause β-cell damage (4, 5).

According to research done so far; diabetes is one of the most important risk factors for ED. In men with diabetes, ED occurs at a younger age than non-diabetics and progresses more rapidly in severity. In fact, type 2 diabetes mellitus has been reported in all studies worldwide; it has been identified as an important factor in the development of ED and one of the complaints that patients with long-term hyperglycemia have is ED. The combination of these two problems is diabetes mellitus erectile dysfunction (DMED). As the number of diabetics increases, so does the number of people DMED, and the combination of these two diseases has many negative effects on people's quality of life (6).

A large number of studies have shown that the incidence of ED in diabetic patients is between 30% and 80%, six times that of normal people, and increases with the age and course of diabetes. The pathogenesis of DMED is complex. Diabetic vascular disease includes macrovascular disease, vascular disease and endothelial dysfunction, all of which are related to the pathophysiological process of ED (7-9).

Hypoglycemia is also common in people with diabetes who have vascular problems, but there is still little evidence that hypoglycemia can lead to sexual dysfunction (10).

The prevalence of ED in men with diabetes is 2 to 3 times higher than in non-diabetics (11) and 10 to 15 years earlier in diabetic men than in non-diabetics (12).

ED may occur in the early stages of diabetes and may even be the main complaint of diabetics in some cases, however, about 95% of these cases can be successfully treated with medication (11); so identify and pay attention to this disorder and its causes will be very useful. The most important factors contributing to ED in diabetics include hypertension, obesity, dyslipidemia, smoking and neuropathy (1). ED in diabetic men is usually caused by neuropathic factors or vascular insufficiency. However, non-diabetic factors sometimes cause sexual dysfunction in these patients (7, 9, 13).

The risk of developing ED in people with diabetes increases with increasing time to diabetes and lack of proper control of blood sugar and the presence of other risk factors such as blood pressure and smoking and high blood fats (14).

The prevalence of ED in people over 18 is more than 8.5%, which is about 422 million people in the world (5). About 5-10% of people with type 1 diabetes and 95-90% have type 2 diabetes. ED occurs in diabetics with different mechanisms, including vascular problems, nephrolithotomy, hormonal imbalances, and psychological problems (14).

In addition to diabetes, there have been numerous human and animal studies that have shown the abnormal effects of lipid-related tests on ED, especially when associated with diabetes. Generally, dyslipidemia is a risk factor for ED patients who also suffer from diabetes (15).

Decreased testosterone and ED are seen in men with type 2 diabetes. An RCT study examined the effect of NFG on serum testosterone levels and ED in diabetic men. TT, FT and IIEF were measured and compared at the beginning of the study and after treatment. The results showed that the levels of these two hormones, as well as IIEF, increased after treatment and NFG was significantly effective in improving ED and testosterone decline due to type 2 diabetes (9).

Hormonal disorders are not common in young men, but sometimes there may be Klein-Felter syndrome or congenital disorders of hypogonadotropic hypogonadism, which can be diagnosed with the help of hormonal test results (2).

ED in diabetic patients is usually caused by underlying neuropathic factors, and these people also show several other neuropathic manifestations (9, 16).

ED is a common symptom of diabetic men. The severity of diabetes, the duration of the disease, and the type of antidiabetic drugs seem to have nothing to do with the incidence of ED, and visceral neuropathy, including the supply of autonomic nerves, supply to the genitalia, maybe the first pathogenic event. Obstructive vascular disease may also be effective. Most studies have shown that endocrine factors do not play a role in impotence in diabetic men (1, 17).

Despite these findings, ED in diabetic patients may not always be related to diabetes. It is reported that in diabetic patients, ED leads to the discovery of macroprolactinemia. Although the diagnosis of prolactinoma has not been confirmed by immunoperoxidase staining or tissue culture studies of adenoma tissue, many of the reported clinical features are similar to those previously described in patients with prolactinoma. Bromocriptine after surgery will cause the plasma prolactin to drop rapidly to close to the normal level, which is related to the increase of plasma testosterone level and increased efficacy (9, 14, 17, 18).

Dialysis patients often suffer from ED. The prevalence of this symptom during dialysis is as high as 90%. Diabetes, diffuse vascular disease and drug therapy are important causes of this disease that severely impairs the quality of life. Due to the high frequency of erectile dysfunction in patients with uremia, the least diagnostic method is usually used. However, accurate differential diagnosis of dialysis patients is also necessary to determine the etiology and modifiable patterns (19, 20).

Considering the ever-growing of omics data (21), data integration and analysis approaches are great keys for solving the complexities of the disorders. In this work, in addition to differentially expressed genes between control and diabetic rats, we explored genes via gene regulatory network inference. The genes, indicating hubs within the network, are supposedly to be

key units controlling a wide range of essential cellular functions in a specific process like sexual dysfunctions.

In this study, the relationship between genes and diabetes and ED and the study of gene networks were investigated in the rat model. Then the purpose of the present study was to identify key genes associated with diabetes and ED.

Materials and Methods

Used datasets and pre-processing

In this work, we collected samples of 10 control and diabetic rats (Affymetrix Rat Expression 230A Array). After a search in NCBI Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/gds), series with accession number GSE2457 consisting of 5 normal and 5 diabetic rats were collected.

In the intended experiment, the gene expression in control and diabetic male Fischer 344 rats (Taconic Farms) has been evaluated. They used streptozotocin to make rats diabetic. Ten weeks later, diabetes and ED have occurred (22).

Raw CEL files of these samples, based on the platform of GPL341, were normalized with robust multi-array average (RMA) expression measure method by using the linear models for microarray data (LIMMA) R package (23) (R software v. 3.2.5). After removing ambiguous probes, the extracted probe IDs were transformed into 10451 unique and validated official gene symbols. After normalization, differentially expressed genes (DEGs) were identified between control and normal penile mucosa if the expression level alteration was above the defined threshold (<0.5 and *p*-value <0.05) by employing the LIMMA R package. The defined threshold prevents withdrawing genes with a lower differential alteration. DEGs were classified by utilizing KEGG to underlying pathways by Enrichr (24).

Assessing regulatory interactions and topological analysis

The expression values of DEGs were used to construct a gene regulatory network (GRN), by the GENEI3 R package (25). To cover DEGs between control and diabetic samples and more sparsity, only the 100 top ranking edges were visualized in Cytoscape (v. 3.4.0). To analyze the topology of constructed GRNs, betweenness centrality (the percentage of times a node appears on the shortest path between all pairs of nodes in the network), as a network centrality parameter, was calculated. Genes with higher betweenness centrality scores, as globally connected genes, were then identified, through the CytoNCA (26). We then took the commonality of DEGs genes (adjusted P-value < 0.05) and high-top ranking genes from CytoNCA via a predicted interaction network using GeneMANIA (27) as the most likely important genes in erectile dysfunction.

Results and discussion

After normalization, differentially expressed genes (DEGs) were identified between control and normal penile mucosa if the expression level alteration was above the defined threshold (<0.5 and *p*-value <0.05) by employing the LIMMA R package.

DEGs analysis

To determine DEGs between diabetic rats with ED and controls, the publicly available microarray dataset GSE2457 was accessed from the GEO database and differences in expression were determined using the limma package. Among the 374 DEGs studied, 146 genes showed increased and 228 genes decreased expression (P<0.05 and |logFC| >0.5).

In Figure 1 the Volcano plot of differentially expressed genes between control and diabetic rats with erectile dysfunction (ED) has been demonstrated.

A volcano plot is often used to display the gene expression experiments. The design of the volcano is a scatter plot showing the relationship between statistical significance (p-value) and the fold change. This allows rapid visual identification of genes with large changes, which are also statistically important. These may be the most important biological genes. In this volcano plot, relative to control, the most increased expression genes are adjusted to the left, the most decreased expression genes are adjusted to the right, and the most important genes are statistically up. Also, the difference in expression of low-area genes is not statistically significant (28, 29).

According to the Volcano plot, the dpp4 gene has shown to down-regulation in diabetic rats. The dpp4 gene encodes dipeptidyl peptidase 4, which is the same as the protein 2 adenosine diaminase complex and CD26 T cell activation antigen. It is an intrinsic membrane glycoprotein and serine exopeptidase that can cleave the proline X dipeptide from the N-terminus of the polypeptide. Dipeptidyl peptidase 4 is highly involved in the metabolism of glucose and insulin and the regulation of the immune system and in a human this gene is located on chromosome 2 (30, 31).

Inhibition of DPP4 results in higher bioavailability of these proteins, thus prolonging the half-life of insulin action. DPP4 inhibitors prevent the degradation of GLP-1 by inhibiting this enzyme and increase the blood concentration of GLP-1 (32, 33).

However, researchers have discovered that the protein product of this gene is also associated with COVID-19 disease. A small but significant number of people with ancient gene variants are extinct, which may double or even quadruple the risk of serious complications from COVID-19. These findings provide information on the enzyme DPP4. The protein allows the

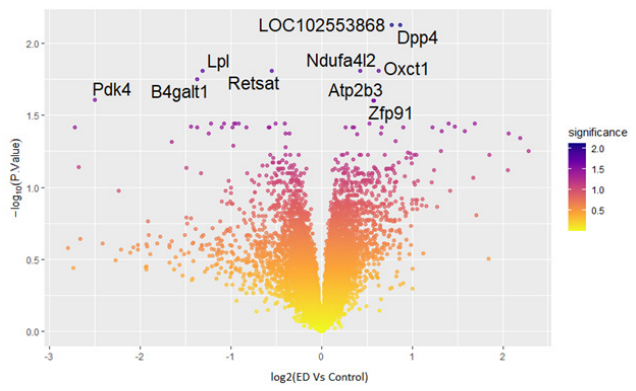

Figure 1. Volcano plot of differentially expressed genes between control and diabetic rats with erectile dysfunction (ED) (P-value < 0.05).

coronavirus, another cause of Middle East Respiratory Syndrome (MERS), to attach to and enter human cells. Analysis of variants of the dpp4 gene in COVID-19 patients shows that this enzyme also provides a second gateway in human cells for the entry of SARS-CoV-2. The normal route of entry of the coronavirus into human cells is through the receptors of the angiotensin-converting enzyme (ACE-2) on the cell surface (34). So based on these results, people with diabetes who have been shown to be more likely to develop erectile dysfunction may be at higher risk for COVID-19 (34).

In addition dpp4, other genes that showed increased expression in diabetic rats with erectile dysfunction include LOC102553868 (uncharacterized), Ndufa412 (NADH dehydrogenase (ubiquinone) I alpha subcomplex, 4-like 2), Oxct1 (3-oxoacid CoA-transferase 1), Atp2b3 (ATPase plasma membrane Ca2+ transporting 3) and Zfp91 (zinc finger protein 91).

Other genes that showed a significant decrease in expression in this gene network include Andpro (androgen-regulated protein), Lox (lysyl oxidase), G0s2 (G0/G1switch 2).

Andpro is one of the most abundant and specific genes expressed in renal proximal tubular epithelial cells. It is precisely regulated by thyroid and sex steroid hormones (mainly androgens) (35). Therefore, reducing the expression of this gene in diabetic samples with ED seems reasonable.

The association of the Lox gene with diabetes has been previously reported. So that inhibition of diabetes-induced Lox overexpression prevents retinal vascular lesions associated with diabetic retinopathy (36).

Also, according to the Volcano plot the Lpl (lipoprotein lipase), Retsat, B4galt1 and Pdk4 genes showed up-regulation in diabetic rats.

Lipoprotein lipase plays an important role in the breakdown of fats into triglycerides, which are transported from organs to the blood through various molecules called lipoproteins. Lpl gene has been known as a gene for insulin resistance (37-38).

Other genes that showed a significant increase in expression in this gene network include Cp (ceruloplasmin), Pdk4 (pyruvate dehydrogenase kinase 4), Hmgcs2 (3-hydroxy-3-methylglutaryl-CoA synthase 2) and Myh8 (myosin heavy chain 8).

The defined threshold prevents withdrawing genes with a lower differential alteration. DEGs were classified by utilizing KEGG to underlying pathways by Enrichr (24) (Figures 2 and 3).

Analysis of pathway enrichment

One interesting observation was the enrichment of extracellular matric (EMC)-receptor interaction in down-regulated genes in a diabetic with ED rats. The role of ECM has been shown in penile activity and functioning, fibrosis and smooth muscle cells (SMC) content (PMID: 29502979) (39).

Based on the most significant P-values, the top five GO terms and KEGG pathways were selected. According to the KEGG diagram, genes involved in terms of PPAR signaling pathway and fatty acid degradation revealed the highest expressions (Figure 2) and genes involved in terms of absorption and AGE-RAGE signaling pathway in diabetic complications showed the lowest down-regulations (Figure 3).

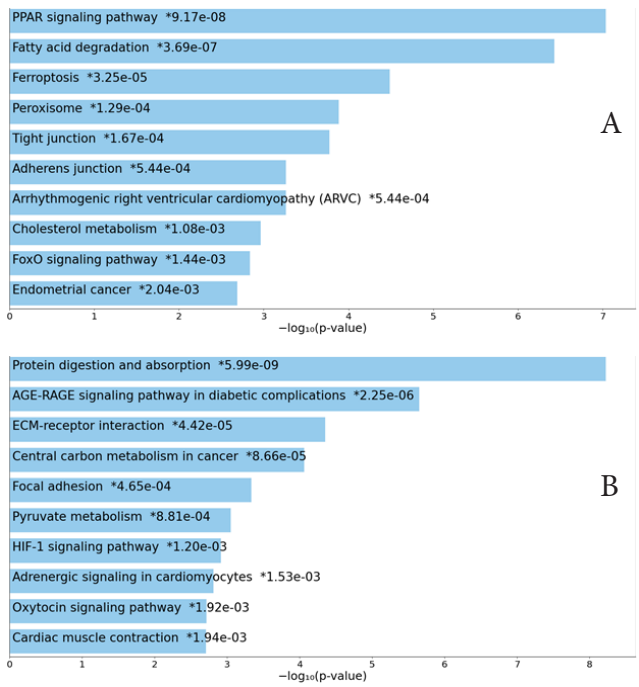

Figure 2. A. The KEGG pathway enrichment analyses of DEGs. KEGG pathway of up-regulated genes in the diabetic with ED rats (adjusted P-value < 0.05). The count represents the number of DEGs enriched in each term. **B.** The KEGG pathway enrichment analyses of DEGs. KEGG pathway of down-regulated genes in the diabetic with ED rats (adjusted P-value < 0.05). The count represents the number of DEGs enriched in each term.

Assessing regulatory interactions and topological analysis

The expression values of DEGs were used to construct a gene regulatory network (GRN), by the GENEI3 R package. To cover DEGs between control and diabetic with ED samples and more sparsity, only the 100 top ranking edges were visualized (Figure 3).

To analyze the topology of constructed GRNs, betweenness centrality, as a network centrality parameter, was calculated. Genes with higher betweenness centrality scores, as globally connected genes, were then identified, through the CytoNCA. We then took the commonality of DEGs genes (adjusted P-value < 0.05) and high-top ranking genes from CytoNCA via a predicted interaction network using *GeneMANIA* as the most likely important genes in erectile dysfunction (Figure 4).

Among the 374 differentially expressed genes (DEG) studied, 146 DEGs expressions was up-regulated, and 228 DEG expression was down-regulated. According to the Volcano plot, the dpp4, LOC102553868, Ndufa412, Oxct1, Atp2b3, Andpro, Lox, G0s2 (G0/G1switch 2) and Zfp91 gene down-regulated and Lpl, Retsat, B4galt1, Cp, Pdk4, Hmgcs2, Myh8 and Pdk4 genes up-regulated in ED and diabetic rats. In addition, genes like dpp4 act as a hub in the inferred GRN. One interesting observation was the enrichment of extracellular matrix (EMC)-receptor interaction in down-regulated genes in a diabetic with ED rats. The role of ECM has been shown in penile activity and functioning, fibrosis and smooth muscle cells (SMC) content. Genes involved in terms of PPAR signaling pathway and fatty acid degra-

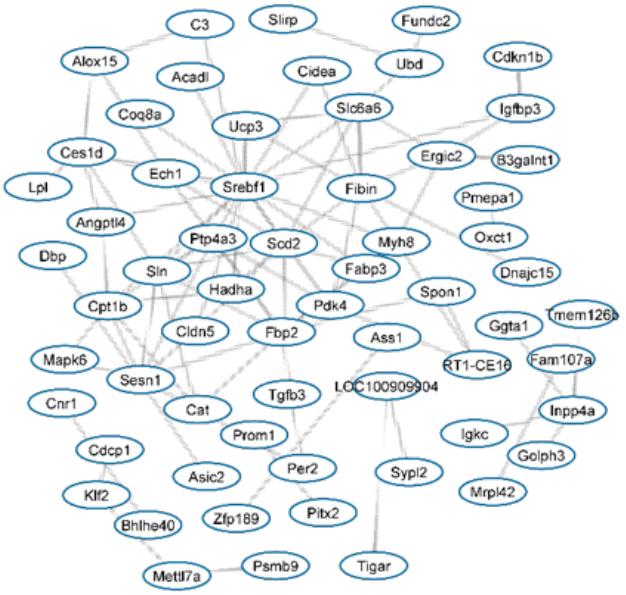

Figure 3. Reconstructing a gene regulatory network using differential expressed genes between control and diabetic with ED rats.

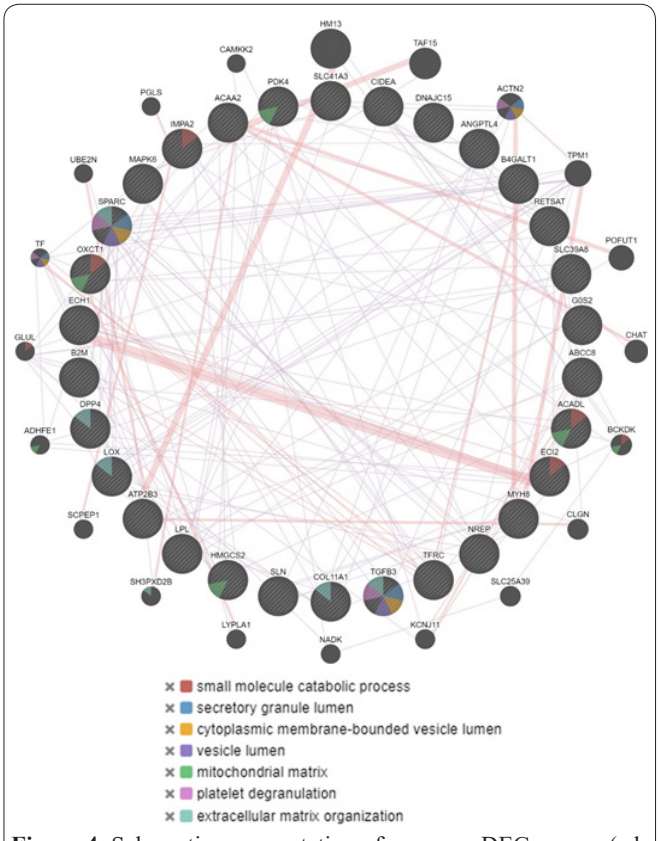

Figure 4. Schematic representation of common DEGs genes (adjusted P-value < 0.05) and high-top ranking genes from CytoNCA by GeneMANIA server control and diabetic with ED rats.

dation revealed the highest expressions

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Conflicts of Interest
The authors declare no conflict of interest.

Ethical Approval
This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent
This article does not contain any studies with human participants.

References

1. Nisahan B, Kumanan T, Rajeshkannan N, Peranantharajah T, Aravinthan M. Erectile dysfunction and associated factors among men with diabetes mellitus from a tertiary diabetic center in Northern Sri Lanka. BMC Res Notes 2019; 12(1): 210.
2. Ludwig W, Phillips M. Organic causes of erectile dysfunction in men under 40. Urolog Int 2014; 92(1): 1-6.
3. Azeez, S., Jafar, S., Aziziaram, Z., Fang, L., Mawlood, A., Ercisli, M. Insulin-producing cells from bone marrow stem cells versus injectable insulin for the treatment of rats with type I diabetes. Cell Mol Biomed Rep 2021; 1(1): 42-51.
4. Dias WB, Hart GW. O-GlcNAc modification in diabetes and Alzheimer's disease. Mol BioSys 2007; 3(11): 766-772.
5. Kumar N, Unnikrishnan B, Thapar R et al. Distress and Its effect on adherence to antidiabetic medications among type 2 diabetes patients in Coastal South India. J Nat Sci Biol Med 2017; 8(2): 216.
6. Li X, Zhao Q, Wang J et al. Efficacy and safety of PDE5 inhibitors in the treatment of diabetes mellitus erectile dysfunction: Protocol for a systematic review: Erratum. Med 2018; 97(44): e13203.
7. Kuneinen S, Kaaja RJ, Vahlberg TJ, Korhonen PE. Metabolic syndrome is not associated with erectile dysfunction in apparently healthy men. Prim Care Diabetes 2020.
8. Jumani DK, Patil O. Erectile dysfunction in diabetes mellitus: A review. J Diabetol 2020; 11(1): 1.
9. Wu Y, Yang C, Meng F et al. Nerve growth factor improves the outcome of type 2 diabetes-induced hypotestosteronemia and erectile dysfunction. Reprod Sci 2019; 26(3): 386-393.
10.Lau D, Kommu S, Mikhailidis D, Morgan R, Mumtaz F. Re: the prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol 2005; 173(3): 1050-1050.
11.Pastuszak AW. Current diagnosis and management of erectile dysfunction. Curr Sex Health Rep 2014; 6(3): 164-176.
12.Levy J. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. Br J Diabetes Vasc Dis 2002; 2(4): 278-280.
13.Kazemi E, Zargooshi J, Kaboudi M et al. A genome-wide association study to identify candidate genes for erectile dysfunction. Brief Bioinforma 2021;22(4):bbaa338. https://doi.org/10.1093/bib/bbaa338
14.Shah PC, Trivedi NA. A meta-analysis on efficacy and tolerability of sildenafil for erectile dysfunction in patients with diabetes mellitus. Indian J Sex Transm Dis AIDS 2018; 39(1): 1-6.
15.Ben Khedher MR, Abid M, Jamoussi K, Hammami M. Comprehensive insight into functional interaction between GNB3 C825T and eNOS T-786C, G894T gene polymorphisms and association with susceptibility to diabetic erectile dysfunction. Andrology 2018; 6(6): 865-873.
16.Ho JH, Adam S, Azmi S et al. Male sexual dysfunction in obesity: The role of sex hormones and small fibre neuropathy. PloS one 2019; 14(9).
17.Raharinavalona SA, Chevalier N, Gruel C, N'Toutoum A C,

Velayoudom Cephise FL. What is the best biological parameter to predict erectile dysfunction in men over 55 years old with type 2 diabetes? J Diabetes Investig. 2020 Jan; 11(1): 170–173.
18.Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. J Sex Med 2008; 5(9): 2125-2134.
19.Piccoli GB, Bermont F, Magnano A, Soragna G, Terzolo M. Prolactinoma in a diabetic dialysis patient with erectile dysfunction: A difficult differential diagnosis. Rev Diabet Stud 2006; 3(4): 200.
20.Hamed SA. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. Expert Rev Clin Pharmacol 2019; 12(1): 61-90.
21.Khosravi P, Gazestani VH, Pirhaji L et al. Inferring interaction type in gene regulatory networks using co-expression data. Algorithms Mol Biol 2015; 10(1): 1-11.
22.Sullivan CJ, Teal TH, Luttrell IP, Tran KB, Peters MA, Wessells H. Microarray analysis reveals novel gene expression changes associated with erectile dysfunction in diabetic rats. Physiol Genomics 2005.
23.Ritchie ME, Phipson B, Wu D et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015; 43(7): e47-e47.
24.Chen EY, Tan CM, Kou Y et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinforma 2013; 14(1): 1-14.
25.Huynh-Thu VA, Irrthum A, Wehenkel L, Geurts P. Inferring regulatory networks from expression data using tree-based methods. PloS One 2010; 5(9): 1-10.
26.Tang Y, Li M, Wang J, Pan Y, Wu F-X. CytoNCA: a cytoscape plugin for centrality analysis and evaluation of protein interaction networks. Biosyst 2015; 127: 67-72.
27.Franz M, Rodriguez H, Lopes C et al. GeneMANIA update 2018. Nucleic Acids Res 2018; 46(W1): W60-W64.
28.McDermaid A, Monier B, Zhao J, Liu B, Ma Q. Interpretation of differential gene expression results of RNA-seq data: review and integration. Brief Bioinforma 2019; 20(6): 2044-2054.
29.Schrode N, Seah C, Deans PM, Hoffman G, Brennand KJ. Analysis framework and experimental design for evaluating synergy-driving gene expression. Nat Protoc 2021: 1-34.
30.Olivares M, Schüppel V, Hassan AM et al. The potential role of the dipeptidyl peptidase-4-like activity from the gut microbiota on the host health. Front Microbiol 2018; 9: 1900.
31.Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action. Diabetes Care 2007; 30(6): 1335-1343.
32.Scheen A. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. Diabetes Obes Metab 2010; 12(8): 648-658.
33.Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors. Drugs 2011; 71(11): 1441-1467.
34.Zeberg H, Pääbo S. The MERS-CoV receptor gene is among COVID-19 risk factors inherited from Neandertals. bioRxiv 2020.
35.Albano GD, Amico F, Cocimano G et al. Adverse Effects of Anabolic-Androgenic Steroids: A Literature Review. Paper presented at: Healthcare, 2021.
36.Song B, Kim D, Nguyen N-H, Roy S. Inhibition of diabetes-induced lysyl oxidase overexpression prevents retinal vascular lesions associated with diabetic retinopathy. Invest Ophthalmol Vis Sci 2018; 59(15): 5965-5972.
37.Kazemi E, Zargooshi J, Dehpahni MF, Motlagh HR, Kaboudi M, Kahrizi D, Khazaie H, Mahaki B, Mohammadian Y, Yazdani L. Androgen regulated protein and pyruvate dehydrogenase kinase 4 in severe erectile dysfunction: A gene expression analysis, and computational study of protein structure. Cell Mol Biol 2021;67(2):89-94.
38.Goodarzi MO, Guo X, Taylor KD et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. Diabetes 2004; 53(1): 214-220.
39. Wan ZH, Li GH, Guo YL, Li WZ, Chen L, Zhang YJ. Amelioration of cavernosal fibrosis and erectile function by lysyl oxidase inhibition in a rat model of cavernous nerve injury. J Sex Med 2018;15(3):304-13.