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A Review on The Genetic Backgrounds and Management Behind Common Podiatric Disorders

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Abstract

The goal of this review paper is to analyze the current research conducted on the genetic factors behind the following podiatric disorders: diabetic foot ulcers, neuropathy, and gout, as well as to answer the question, "Where should future research direct their attention in order to improve prevention and complications in diabetic patients?" Foot diseases in diabetic patients significantly decrease quality of life and provoke serious complications in the body, such as infections, amputations, and in some cases, lead to death. Although many causes of these conditions are environmental, genes play a pivotal role in identifying those individuals who are more likely to develop diseases. Current research has only begun to explore which genes may play a role in provoking diabetic foot disorders. However, future research should focus on developing diagnostic exams to discover genetic tests for these individuals who will most likely develop diabetes, particular biochemical and molecular mechanisms that lead to diabetic dysfunction in the lower extremities, and ways to prevent recurring injuries and lesions in affected individuals. Diabetic foot ulcers, neuropathy, and gout research is not advanced as it is in other the medical fields, and scientists should focus more on the mechanisms of each disease and genetic testing to identify individuals who are vulnerable to diabetes.

Introduction

Podiatric medicine is the medical specialty that focuses on the lower extremities, more specifically the foot and ankle. A podiatrist is a professional who examines, diagnoses, and treats foot and ankle disorders **[1].** Careers in podiatry include, but are not limited to, surgery, biomechanics, vascular health, sports medicine, and pediatrics **[2].** Doctors of podiatric medicine receive education that includes four years of graduate school and three years of residency **[2].** A

podiatrist is one of the first medical specialists to discover chronic disorders such as diabetes and cardiovascular disease that frequently start in the lower limbs **[2].**

In addition to a significant practice diversity in various countries, podiatry has a strong medical history. The professional care of feet started back in 2400 BC ancient Egypt, and drawings of surgical procedures can be found in Ankhmahor's Tomb in the Necropolis of Saqqara **[3].** One of the first pictures shows a foot operation being performed on an emperor, cited as proof that surgical medicine was practiced on the feet. Centuries later, podiatrists were combined into organized medicine with the rest of the other specialties (except for the United States, that still gives podiatrists separate degrees called a "DPM") **[3].** The first society of podiatrists was founded in 1895 in New York, and still exists today under the name NYSPMA (New York State Podiatric Medical Association). In 1911, the first podiatric school opened in New York **[3].** Today, Ohio has one of the eleven podiatric schools in the United States, which is associated with Kent State University (formerly called Ohio College of Podiatric Medicine) **[2].**

Particularly in the United States, a podiatrist plays an essential role in treating one major chronic disease that affects millions across the country: diabetes. Figure 1 shows that the number of individuals with diabetes has drastically increased since the COVID pandemic in 2020 **[5]**. According to the CDC (updated November of 2023), 38.4 million people have diabetes in the United States, with 29.7 million people diagnosed and 8.7 million people undiagnosed **[5].** Furthermore, 97.6 million people also have prediabetes, which is 38% of the population. Diabetes alone causes multiple podiatric conditions that can lead to infections, diseases, and amputations **[5].** Although environmental factors play a role in diabetes, this paper will focus on how genetics function in predetermination of the following conditions: diabetic foot ulcers, neuropathy, and gout **[4].** Genetics is important because it may be able to predict who is more

likely to develop podiatric disorders and can identify via tests who might be predetermined for a specific disease **[6].** It is essential for early detection of disorders and prevention. This review paper will cover the genetic information on diabetic foot ulcers, neuropathy, and gout, as well as an analysis on how current research can advance toward the prevention of lower limb disorders.

Part I: Diabetic Foot Ulcers

Common problems podiatrists treat on a daily basis are diabetic foot ulcers. Diabetic foot ulcers are complication from diabetes that involve wounds that the body cannot heal by itself **[10].** Early signs of an ulceration include swelling of the skin, redness, irritation, and drainage from the foot **[4].** Even though diabetic foot ulcers greatly affect patients in the United States, many studies have shown how prevalent they are across the world. Lower extremity ulcers are serious problems that account for amputations in 90% of the diabetics who have them **[8].** Around the world, the leading causes of hospitalization in diabetic patients are ulcerations, infections, and gangrene, each health event costing around $40,000 to treat **[8].** In a lifetime, diabetics have a 25% chance of developing ulcers **[8].** Many additional podiatric ailments such as neuropathy, vascular risk factor, callus formation, and excessive localized pressure dramatically increase the probability of developing ulcers **[8].**

Genetics

Although many of these factors are extrinsic, several current research studies are discovering which genes aid in patient development of diabetic foot ulcers. Due to the amount of scientific information, summaries of each study will be broken down into the following genes that were studied: the TLR2 receptor gene, miRNAs, Vascular Endothelial Growth Factor (VEGF), and single nucleotide variants (SNV) of the ITLN1 gene.

TLR2 Gene

The first significant gene involved in diabetic wound ulcers is the TLR2 receptor gene. A study performed by Journal of Tissue Viability shows that TLR2 controls inflammation during bacterial invasion of **the body synthesizes Cx43 epithelial cells**, to make tight junctions **[8].** Disruption of TLR2 results in changes to Cx43 and poor performance in angiogenesis, inflammation, poor expression of gap junction proteins, and disordered immune responses that result in diabetic patients to heal slowly from their wounds **[8].** In severe cases, amputation is needed to stop mutated TLR2, which makes the open wound more susceptible to infections **[8].** This dysregulation may be due to insufficient healing mechanisms of diabetic foot ulcers, leading to fewer leukocytes and lower angiogenesis performance near the wound. In addition, poor healing could also be accredited to infections and factors that inhibit keratinocytes at the ulcer bed **[8].**

miRNAs

MicroRNAs function to control hypoglycemia. A major factor involved in hypoglycemia is the Metabolic Memory Phenomenon, which states that delaying glucose control in healing develops diabetic complications **[8].** Diabetic phenotypes progress when hyperglycemia-associated epigenetic patterns mutate normal miRNAs. These epigenetic patterns are hereditary and are passed on through mitotic cell division, and the maintenance of hyperglycemia triggers long term complications such as DFU **[8]**. More specifically, these pattern changes involve histone modification via DNA methylation and microRNA expression. These modifications affect various tissues involved in wound healing and result in transcription changes **[8].** Issues with wound healing can go all the way back to miRNAs- 126, 503, and 210 **[8].** Deficiencies in miRNA-126 lead to dysfunctional endothelial cell preparation, migration, and angiogenesis.

Excess amounts of miRNA-503 increase the chances of triggering ischemia, resulting in improper healing. Mutations of miRNA-210 prevent the expression of E2F3, an important transcription factor involved in wound healing **[8].**

Vascular Endothelial Growth Factor (VEGF)

The same study that focused on the TLR2 gene also discussed evidence of vascular endothelial growth factors function in healing ulcers **[8].** VEGF's have become a growing interest of podiatric geneticists, and some studies have shown that polymorphisms may affect the VEGF proteins that control the expression of certain mRNAs **[8].** A study conducted by the International Diabetes Federation investigated their relationship with single nucleotide polymorphisms. More specifically, this study focused on vascular endothelial growth factor receptor 2 (VEGFR-2), which can only be found on endothelial cells. Their main function is to clear the extracellular matrix of endothelial cells to facilitate angiogenesis, and polymorphisms of VEGF have great importance in mRNA expression levels **[10].** Performing this function poorly inhibits wound healing in diabetic patients. Location of this VEGF gene can be found spanning 14kb on chromosome 6, which contains 7 introns and 8 exons **[10]**.

The goal of this study was to determine the relationship between VEGF-2578*C/A and VEGF-7*CT polymorphisms in patients with and without diabetic foot ulcers. There were 247 diabetic patients with ulcers, 98 control patients, and 241 diabetic patients without ulcers. Each patient extracted 3-5 cc of blood for their DNA samples, and a "master" solution of each sample was mixed in with the patients' DNA samples **[10].** The results showed that -7*C/T polymorphism amounts were not different in diabetic versus control patients, but the VEGF gene polymorphism at -2578* is significantly different between all three groups with a p-value of 0.003 **[10].** In patients with diabetic foot ulcers, there was a significantly lower frequency of the

genotype AA **[10].** As a consequence of diabetic foot ulcers, other studies have proven that the A allele low frequency can lead to poor angiogenesis performance **[10].**

ITLN1, HSP and HIF genes

A 2017 study from the Polish Archives of Internal Medicine identified three more genes that contribute to the genetics of diabetic foot ulcers. First, variance of the ITLN1 gene has an impact on the development of DFU **[5].** One unique feature of ITLN1 is that variant rs2274907 is sex-specific to men and are more likely to develop DFUs if they have this single nucleotide variant (SNV) **[9].**

Another discovery from this study is the contribution of heat shock proteins to ulcerations **[9].** A heat shock protein is a type of chaperone protein that is activated by the immune system when the body undergoes a stressful environmental condition. This study found that the HSP70-hom T/T genotype is strongly associated with diabetic foot ulcer patients **[9].** More specifically, functional polymorphism may play a role **[9].**

Lastly, another study discovered that a mutation in exon 12 of the gene HIF-1a rs11549565 causes a decrease in the HIF-1a gene SNV, resulting in a substitution mutation that switches proline to serine by changing a C to a T **[9].** This could also prolong the immune system's healing mechanisms by maintaining a surplus of proinflammatory cytokines **[9].**

Mechanisms and Physiology

Neuropathy is one of the biggest conditions behind diabetic foot ulcers. Long-term hyperglycemia results in neuropathy, leading to metabolic disorders due to the increased activation of polyol glucose along with vascular impairment due to toxic sorbitol in neurons **[8].** Eventually, epithelial cells will lose their function due to constant hyperglycemia, which leads to

an increase in angiogenesis and nitric oxide. Without nitric oxide, there is an increase in ischemia **[8].** This is especially dangerous because it will offer the patient the impression that the open wound is healing, but instead, there is an open area for infections to enter the body, further leading to sepsis or amputation **[8]**. Without a diabetic foot ulcer problem, the immune system utilizes fibroblasts, endothelial cells, phagocytes, platelets, and keratinocytes to heal **[8].**

Furthermore, VEGFs have their own special mechanisms to perform wound healing. Growth factors are important in enabling cellular interaction by acting as second messengers between different cells **[8].** There are also several growth factors that upregulate angiogenesis: epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin 8 (IL-8) **[8].** Figure 2 from the Journal of Tissue Viability displays a good summary of the growth factor mechanisms behind wound healing.

Unfortunately, when there is an ulcer, the body cannot properly regulate wound healing, which is what makes ulcers so dangerous. One major factor that contributes to this problem is tissue hypoxia. Hypoxia is the result of inadequate angiogenesis, which is unfavorable for the wound healing process. Hypoxia can amplify the acute inflammatory response by increasing the levels of oxygen radicals (Reactive Oxygen Species) (ROS) [8]. Another important feature of diabetic foot ulcers is that normal healing processes are blocked due to elevated levels of MMPs. Lastly, ulceration inhibits the following healing mechanisms: growth factor production, angiogenesis, phagocyte activity, collagen deposition, epidermal barrier function, the amount of granulation tissue, keratinocyte and fibroblast migration and proliferation, innervation of the epidermis, and remodeling of bone which is mediated by the MMPs and the extracellular matrix (ECM)] [8].

Treatments

Fortunately, there are several treatment options that can prevent early diabetic foot ulcerations from becoming too severe. There are several factors that can be checked before treating the actual wound. First, a clinical imaging diagnosis must be made to rule out other podiatric conditions **[7].** Second, it is essential to check that no infections exist, and if they do, to treat those first; antibiotics can be taken to resolve infections. Some examples of antibiotics include an aminopenicillin and penicillinase inhibitor combination, quinolone plus either metronidazole or clindamycin, and intravenous options (for soft-tissue infection) include imipenem and gentamicin **[7].** Lastly, any ischemia conditions and injuries due to pressure must be treated **[7].** Once these situations have been addressed, the physician can focus on the wound and future prevention. Some remedies that can heal the wound include, but are not limited to, topical applications, callus removals, wound dressing, and management of peripheral vascular disease and glycemic control **[7, 8].** Off-loading treatments (orthotics) are available, but it is essential to provide another primary form of treatment; too much off-loading can result in muscle atrophy, thrombosis, and secondary ulceration **[7].** No matter the treatments selected by the patient, the main goal is to prevent future ulcerations and infection in the current wound.

Complications

Diabetic foot ulcers are very serious wounds that have major consequences if not properly treated. Unfortunately, many patients with diabetic foot ulcers undergo amputation, which is one of the largest reasons for mortality in diabetics. Although mortality rates vary by country, the numbers are significant; 9% in the Netherlands, 10-15% in the United Kingdom, and up to 50-59% in Sweden and Italy **[7].** The United State have a lower mortality rate compared to Europe, which suggests there is a faster access to treatment, but there are remarkably more cases of

diabetic foot ulcer **[7].** If left untreated, diabetic foot ulcers can result in limited movements, cardiovascular disease, and atherosclerosis in the lower extremities **[7].**

Although infections are usually a complication in diabetic foot ulcer, not treating infections in the wound will delay treatment in healing **[7].** This can result in the ulcer turning progressing to a chronic wound and infect bone. Lastly, lack of awareness to the conditions causes substantial complications to the ulcer; on average, it takes a patient 15 days to realize there is a lower extremity problem **[7].** This delay causes healing without treatment to drop to 40%, and if it does heal on its own, it is a temporary fix due to the ulcer affecting the body's proper healing mechanisms **[7].**

Part 2: Diabetic Peripheral Neuropathy

Diabetic Peripheral Neuropathy (DPN) is a serious condition that results in permanent nerve damage to the peripheral nervous system. DPN most often happens in the lower limbs and feet, but can spread to the upper limbs and hands if left untreated. Although DPN is the least screened diabetic complication, about 50% of diabetic patients develop DPN and can lead to consequences such as amputations and bone infections **[13]**. It is also a risk factor for diabetic foot ulcers, as hyperglycemia can harm nerves and eventually result in open wounds **[15]**. The main concern with DPN is that there have been several trials to discover treatment, but none of the studies have been successful **[14].** In addition to an unknown treatment, there are several additional types of neuropathies that aid in presenting symptoms of DPN. Symptoms vary based on the type of neuropathy and anatomical location, but mainly include sensational pain and numbness in infected areas **[14].** More specific symptoms include leg cramps, excessive thermal

sensation, tingling in the lower limbs, and additional problems in the urinary and cardiovascular symptoms **[14, 15].** Although science has not discovered a definitive genetic cause, there are numerous candidate genes that may be associated with DPN. This section of the review highlights the most common candidate genes found in past research experiments and how they may affect DPN.

Genetics

There are numerous genes that have been accounted in diabetic peripheral neuropathy. This section highlights the most commonly discovered in experiments and most likely to be a risk factor: TKT, Lipoprotein(a), Homocysteine, ACE, EPOE, VEGF, NOS3, SPTLC1, and RAB7 genes.

1. *TKT Genetic Variability*

Transketolase (TKT) is an enzyme involved in the pentose phosphate pathway that removes abundances of glucose from the pathway so the body can avoid "hyperglycemia-induced damage" when initiated by thiamine **[14].** A study published in 2017 found that TKT may be involved in DPN for both diabetic I and II patients, more specifically male patients. Associations with damage to peripheral nerves have been found in mutations of SNP rs62255988 and SNP rs7648309, but outside of this, not much has been found **[14].** Although more studies need to focus on the relationship between thiamine and TKT, research has discovered a connection between TKT, sodium channels, and methylglyoxal - a derivative of pyruvic acid from glycolysis **[14].** Diabetic patients with higher methylglyoxal plasma levels have reported to also have higher pain levels, in addition to variation in the sodium channels involved with methylglyoxal. These mutations have led to a depletion of products from the pentose phosphate pathway **[14].** While

TKT aids in preventing DPN by controlling the pentose phosphate pathway, more studies need to discover the types of polymorphisms that aid in this mechanism **[14].**

2. *Lipoprotein(a) and Homocysteine Genetic Risk Factors*

A study from the Endocrine Journal in 2011 determined that if lipoprotein(a) and homocysteine are genetic risk factors for diabetic peripheral neuropathy and vascular disease in the foot (VDF). This studied concluded that low Lp(a) amounts are associated with diabetic neuropathy and poor wound healing in the foot, while both Lp(a) and Hcy are more at-risk genes for VDF **[12].** Vascular disease of the foot is also important to look at alongside diabetic neuropathy of the foot, because loss of oxygen and blood flow to neural tissues due to diabetes will result in necrosis (cell death) of neurons. Lp(a) is a protein similar to the LDL receptor found in cholesterol, and Hcy is a derivative of methionine with a very reactive sulfhydryl group that causes variations in endothelial cells **[12].** Both have associations with cardiovascular diseases **[12].** This study was divided into three groups and measured the concentrations of Lp(a) and Hcy in each patient: patients with VDF, patients with DPN, and controls; it was found that low Lp(a) levels were with patients with DPN and not with Hcy, which was the most shocking result **[12].** Although more studies need to be done for confirmation, low Lp(a) levels in neuropathic patients could be due to issues with wound healing mechanisms.

3. *Uremic Neuropathy and Cardiac Autonomic Connections to DPN*

In addition to diabetic peripheral neuropathy, there are two more common types that aid in developing DPN symptoms: Uremic Neuropathy (UN), which is neuropathy caused by uremic toxins due to kidney problems, and Cardiac Autonomic Neuropathy (CAN), which affects the nerves that are part of the cardiovascular system **[13].** Each type of neuropathy has overlapping

symptoms, such as hyperglycemia, hypertension, and insulin resistance that result in oxidative stress and gene expression alteration in biophysiological mechanisms **[13].** Every anatomical system works together in the body, and these three neuropathies together can result in negative consequences on your feet. The purpose of Witzel's study (2015) was to identify common genes between the three neuropathies that aid in promoting the disease **[13].** Seven common genes were found between the three conditions, but for the purpose of this article, only four will be reviewed: ACE, EPOE, VEGF, and NOS3 genes. The end of this paper will analyze how the following genes mentioned can be beneficial in future research to find preventative care for diabetic patients.

a. ACE

The ACE gene activates the "angiotensin converting enzyme, which is a vasoconstrictor that converts angiotensin I to angiotensin II" **[13].** Angiotensin II is essential for physiological mechanisms as its function is to mediate glucose and insulin, and angiotensin II does not function properly (i.e., makes more than it should), this results in hyperglycemia, which induces oxidative stress, inflammation, and endothelial cell damage **[13].** An "insertion/deletion mutation of the polymorphism 287 base pair Alu sequence" that results in an increase of angiotensin II has been suggested to be involved with DPN **[13].** However, experiments on this assumption have been very contradicting, so more studies are needed to support this data.

b. APOE

Apolipoprotein (apoE) is a gene found in low-density cholesterol (LDL) which is essential for "lipid metabolism, hypercholesterolemia, as well as nerve repair and regeneration" [13]. There are three main alleles that come from amino acid variations at 112 Cys/Arg (rs429358

C/T) and 158 Arg/Cys (rs7412 T/C): apoE2, apoE3, and epoE4. Each isoform has a different role in physiological mechanisms and diseases as their charges and stability differ **[13].** While the E4 variant reacts more to environmental changes, E2 may have a defensive role in neuromuscular mechanisms in disease **[13].** However, no exact connection has been made.

c. VEGF

Vascular Endothelial Growth Factor (VEGF) has been known for beneficial roles in organ and tissue repair, in addition to being included in previous diabetic foot ulcer studies. While VEGF may play a role in protecting neural function and tissue regeneration, other studies have shown that high VEGF levels can result in cardiovascular issues and diabetic complications **[13].** Most studies have confirmed that half of VEGF variation in occurrence comes from the SNPs rs6921438 and rs10738760 **[13].**

d. NOS3

Nitric Oxide is a vasodilator that comes from nitric oxide synthase (NOS3) and is important in homeostasis and endothelial cell function **[13].** DPN studies have focused on nitric oxide due to their physiological roles in the peripheral nervous system. Three genetic polymorphisms of nitric oxide have been associated with diabetic complications: -786 T/C (rs2070744), 894 G/T (rs1799983) SNPs, and the variable number tandem repeat (VNTR) polymorphism **[13].** Opposing results have also been reported with nitric oxide and DPN, and many researchers believe this is due to environmental effects **[13].**

Hereditary Sensory Neuropathy (HSN)

A rare type of neuropathy is called Hereditary Sensory Neuropathy, which affects the sensory neurons of the nervous system. Differentiating symptoms include progressive sensory

loss and malnourished nails **[11].** Although rare, there are several candidate genes that are associated with HSN. This section will focus on the SPTLC1 gene, discussed in another article by Auer-Grumbach et al (2005).

A. SPTLC

Serine Palmitoyl Transferase Long-Chain Gene (SPTLC1) is a key enzyme in sphingolipid regulation mechanisms and has two subunits: SPTLC base subunit 1 and 2 located in the endoplasmic reticulum of a cell **[11].** SPTLC 1 spans across 15 exons, and previous research has discovered missense mutations located on chromosome 9q22 that are associated with HSN **[11].** The most common mutation can be found on the fifth exon in that 15-exon stretch of the gene, which is normally a cysteine to tryptophan substitution mutation **[11].** This result was found in families from Portugal and Czechia, suggesting that this gene is hereditary **[11].** However, this is limited information due to small sample sizes and little experimentation.

Mechanisms and Physiology

Due to the significant number of genes involved in Diabetic Peripheral Neuropathy, there are several biochemical and physiological mechanisms involved in developing this condition. Most research have found pathology to be a cross between signaling pathways that promote chronic issues such as hypertension, obesity, and dyslipidemia that result in mitochondrial dysfunction and oxidative stress **[14].** Long term hyperglycemia results in an increase of toxic sorbitol in cells from glucose metabolism pathways, resulting in vascular and nervous tissue damage **[7].** Although hyperglycemia is a beginning to discovering the genetics behind DPN, this cannot be the only condition to consider, which is why it is essential to perform more genetic testing. While there are several genes that could be candidates for causing diabetic peripheral

neuropathy, many studies either contradict other experiments or were unable to identify the specific polymorphisms involved. While there is still much to discover mechanistically, many genes that influence diabetic complications are linked to biochemical changes involving glucose and inflammation **[7].**

Treatments

Although research is still looking for an exact preventative treatment against DPN, there have still been advancements in diagnosis and prevention of DPN from worsening. To prevent serious complications from DPN, it is essential for patients and healthcare providers to learn how to detect early signs and participate in frequent testing, even if a diabetic patient is asymptomatic. Some current DPN assessments include nerve conduction velocity testing of the lower limbs, thermal sensation assessments, and devices that can record unusual signals in neuron fibers and axon degeneration **[13,14].** Physical exams can also be used to detect early onset of DPN. Although these studies can be limited, it is important to measure any neural damage that can be quantified in order to promote prevention.

While modern treatments involve a change in diet and physical activity and monitoring glucose levels, there is no long-term preventative treatment for DPN and do not necessarily stop progression of the disease **[13].** Certain drugs, such as thiamine are under current investigation to treating DPN **[13].** Current studies are attempting to use Next Generation Sequencing (NGS) to identify genetic variants that cause DPN **[12].** Although there are several candidate genes that may cause DPN, science has a long road in discovering the exact cause and appropriate course of treatment.

Complications

Diabetic Peripheral Neuropathy is a slow, progressive disease that results in severe complications and extreme costs to a patient's quality of life **[14].** While DPN starts off asymptomatic, the pain becomes more prominent in the later stages of the disease. Consistent hyperglycemia leads to epithelial cell and neural cell damage **[12].** Eventually, patients develop foot deformities, bone infections, sensory loss, and osteomyelitis. If left untreated, DPN results in necrosis, Charcot arthropathy (bone weakening and breaking), and amputations **[11,14].** Diabetic Peripheral Neuropathy is a significant condition that not only kills the main functions of the human body, but DPN brings extreme financial, emotional, and social costs to the patient. It is critical that current research shifts their focus on finding a genetic cause for DPN to provide early prevention for patients.

Part 3: Gout

Introduction (Background/Symptoms)

Gout is a specific type of arthritis that causes inflammation in the joints due to buildup of urate crystals in certain regions of the body **[15, 16].** Symptoms include sudden, severe joint pain, swelling, tenderness, pain the first phalanx, and hyperuricemia **[18].** Gout is often a result of hyperuricemia, a condition in which the blood contains too much uric acid due to a high serum rate **[18].** Prevalence of gout varies between populations, as New Zealand Māori, Pacific Islanders, and Taiwanese have the most patients with this condition; it is also found more often in males, with 40% of men in these populations diagnosed with gout **[18].** Many studies have shown that gout is an incredibly complex disease in which multiple genes a significant role.

Although gout can affect any joint in the body, it is most commonly found in the first metatarsal bone of the foot. A study in 2011 found that 56-78% of patients develop initial symptoms of gout in the foot **[18].** This could be due to an accumulation of urate crystals in the synovial fluid of the feet **[18].** Lower-limb specific symptoms of gout include cartilage tearing, inflammation, and severe curving of the foot **[19].** This condition starts off as asymptomatic, then symptoms appear suddenly. As symptoms progress, patients suffer from slower walking times, pain while walking and placing extreme pressure on the foot **[19].** This section focuses on the genetics, mechanisms, and maintenance of gout that have been found in past and current research.

Genetics

Currently, not much is known about the genetics involved in gout. However, there are three key genes that have been identified and will be explained in this section: GLUT9, ALDH2/ALDH16A1, and the NLRP3 inflammasome pathway.

GLUT9

The SLC2A9 (GLUT9) gene is "a renal transporter that reabsorbs urine from the urine filtrate" **[16].** Several variants of the GLUT9 exist, and the most common are URAT1, ABCG2, and ABCG4 **[15].** Many studies have found that having any one of these variants results in a loss of function for the gene, resulting in less regulation of urate crystals, an accumulation of crystals in the joint, leading to gout **[15].** Actions affecting urate crystals all depend on the variant a patient possesses. For example, ABCG2 and ABCG4 are associated with developing gout, while having more URAT1 variations lower the chances of gout. ABCG2 and ABCG4 are transporters that regulate urate in the body and mainly appear when urate is above or below normal amounts

to bring urate back to normal **[16].** Lower amounts of ABCG2 and ABCG4 in the stomach are associated with gout, but more studies need to be done to confirm this **[17].** Mutations in the ABCG2 and ABCG4 genes are mainly found in European and East Asian populations **[16].**

ALDH2 and ALDH16A1

GWAS studies have discovered strong connections between gout and aldehyde dehydrogenase genes **[16].** Aldehydes are important physiologically, as they interact with proteins in several mechanisms. ALDH2 has been shown to influence hypoxanthine-guanine phosphoribosyl transferase (HPRT1), a protein that processes urate **[17].** A missense mutation in the ALDH16A1 gene prevents this enzyme from functioning normally, resulting in higher chances of developing gout **[16].** A 2017 study found a homolog gene to ALDH2 in mice, the Aldh16A1; a **knockdown** in this gene increased expression of two other genes (Slc16a9 and Abcc4) and decreased the frequency of Slc17a3 gene, all of which contribute to serum urate control **[16].** Another popular variant of the ALDH2 is the rs671 variant, which contains a lysine allele. Interestingly, this variant reduced the chances of gout; however, it was only found in Asian populations **[16].** It was also found that those who drink alcohol inhibit the affects of rs671, thus increasing their chances of gout **[16].**

NLRP3 Inflammasome

NLRP3 is an inflammasome expressed by humans that take part in the immune system and increase in signaling when the body is fighting a disease **[16].** Several genes influence this protein and its actions on the body. For example, higher mRNA expression in the TLR4 gene increases the chances of gout **[16].** A missense mutation of the Gln allele in the PPARGC1B gene increases gout and also decreases the number of mitochondria that function containing this gene

[16]. Lastly, CARD8 influences the IL-beta 1 gene in the immune system, which works closely with NLRP3. A decrease in gene expression of CARD8 results in an increase in IL-beta 1, reducing the probability of developing gout **[16].**

Mechanisms

While research must advance to discover more genes involved in gout, information is known about the environmental and biochemical mechanisms behind gout. The main cause of gout comes from hyperuricemia, which develops due to increased amounts of serum urate in the bloodstream **[17].** Unhealthy foods are digested and change into urate, and an abundance of junk food increases the amount of urate crystals in the blood **[17].** When there is an imbalance of urate crystals and healthy tissues, the crystals move around the bones and joints, causing swelling and inflammation **[16].** In the foot, this accumulation moves the synovial fluid that separates joints out of its normal area, and this loss of fluid also contributes to the swelling **[16].**

The genetic influences of NLRP3 play a strong role in influencing the immune system. Dysfunctional NLRP3 inflammasomes decreases the amount of white blood cells, which means the responses to urate crystals do not exist **[17].** This in turn can also result in antibody mutations that contribute to the increase in urate crystals. Mutants of TRL4 genes play a role in antibody variants **[17].**

Lastly, environmental factors that dysregulate normal biochemical mechanisms also play a role in the development of urate crystals. For example, cartilage degeneration occurs and also contributes to gout in the foot. The most common environmental methods that influence crystal growth are trauma and temperature changes. Studies have shown that cold temperatures can

promote the growth of already existing crystals, and minor injuries such as stubbing a toe or dropping something on your foot are risk factors for developing crystals **[16].**

Treatments

Treatment for gout is patient dependent, multifactorial, and long-term. Acute cases of gout usually go away on their own within a few weeks, but sometimes a steroid is injected in the foot to decrease pain symptoms **[17].** When patients are put on a medication for gout (or any type of arthritis), it is typically a continuing treatment **[18].** Gout is most often diagnosed by a podiatrist or primary care physician, and it is important for the patient to make appointments even after the gout is treated **[16].** Although a change in diet has not been shown to greatly change the amount of serum urate in the blood, a significant change in weight loss has impacted serum urate levels **[18].** The most popular drug for gout is allopurinol, which lowers the amount of urate crystals and targets the kidneys to prevent excess production of urate **[17].** Some patients are not able to take allopurinol due to side effects on the kidneys, so other drug treatments include febuxostat, probenecid, and lesinurad, which all help regulate urate serum **[18].**

Complications

Acute conditions of gout often dissipate on their own and/or with a steroid injection; it is the chronic stage of gout that can have severe consequences. Endothelial cell oxidative stress, chronic kidney disease, cardiovascular disease, obesity, and diabetes can all be the result of untreated gout **[16,17].** Gout can also turn into a condition called “tophaceous gout,” which results in severe foot pain, numbness, and the spread of crystals to other joints of the body **[17].**

Part 4: Analysis – What Future Research Should Pursue

The purpose of this review paper is to summarize current and past research on common podiatric disorders (diabetic foot ulcers, diabetic peripheral neuropathy, and gout) and create an analysis to answer the question, "Where should future research focus to discover and create better prevention and treatment for patients?" This section addresses this question.

Analysis on DFU

Out of the three diseases mentioned in this review, diabetic foot ulcers have the most visual cues to identify its condition. This can be used to medicine's advantage by promoting diabetics to have monthly appointments with podiatrists and/or primary care physicians. Genetically, two genes that research should further explore are Vascular Endothelial Growth Factor (VEGF) and microRNAs.

First, VEGF aids in wound healing and tissue repair. Although genes cannot be created with pharmaceutical drugs, it may be possible to create a treatment that intervenes with the VEGF and angiogenesis mechanisms to help a patient's lower limbs improve its own wound healing. Genetic research should also focus on testing to discover what stimulates and inhibits the regulation of VEGF environmentally to find a treatment based on epigenetics.

Another area research should continue to investigate in the world of genetics is miRNAs. Many miRNAs function to help cells with wound healing; however, conditions that result in diabetic foot ulcers, such as hyperglycemia, dysregulate miRNAs and inhibit their abilities in healing mechanisms. Although hyperglycemia is one of the main causes of this, it does not apply to everyone; more genetic testing needs to be done to identify more possible causes of miRNA loss of function.

Analysis on DPN

Diabetic Peripheral Neuropathy (DPN) has the most genetic information out of the three conditions; however, very little is known about treatment. This could be due to the irreversible damage of nerve cell death, which is the main consequence of having DPN. Although you cannot reverse neuron cell death, research has the potential to prevent DPN form reaching this point; three pieces of genetic material that may possibly aid in the prevention of DPN are nitric oxide, lipoprotein(a), and homocysteine.

The first interesting DPN project research can look at is increasing nitric oxide expression in the body (NO). Nitric oxide is a vasodilator, meaning it increases the diameter of blood vessels and encourages more blood flow. Blood flow and a healthy cardiovascular system is essential to having a healthy nervous system; without blood flow, necrosis occurs (cell death), and this includes neurons. Diabetics (especially type II patients) have issues with promoting blood flow to their peripheral blood vessels due to excessive amounts of glucose in the blood and weight gain. This results in the damaging and bursting of blood vessels, as well as a loss of oxygen to surrounding tissues. If nitric oxide increases vasodilation, then more blood can be brought to peripheral arteries and provide cells nutrients they need to survive, therefore preventing DPN.

Two other risk factors that can help with the prevention and management of DPN are lipoprotein(a) and homocysteine. Lp(a) is similar to the receptors found in cholesterol, and homocysteine functions in endothelial cells. Similar to nitric oxide, both molecules work closely with cardiovascular issues. Genetic research should focus on performing **gene knock down/knock** in testing to determine what mechanisms and pathways that influence the amount of lipoprotein(a) and homocysteine.

Analysis on Gout

In contrast to diabetic peripheral neuropathy, gout has pharmaceutical treatments, but minimal information on genes and mechanisms involved, especially in the podiatric field. Although few common genes have been associated with gout, very little is known about the genetic variants. Similar to DPN, research should focus on experiments that **knock down/knock in genes** and identifying pathways that influence urate crystals, more specifically in GLUT9. Another challenge with gout (and the rest of these conditions) is lack of education and awareness to patients. Many diabetic patients are unaware of the consequences of prolonged gout, and often are not consistent with administering treatment. Not only does there need to be more genetic testing for GLUT9 mechanisms in gout, there needs to be some type of educational system in healthcare so patients can learn to identify early signs of diabetic conditions and prevention.

Conclusion

Podiatric disorders are common but often overlooked, resulting in severe complications if left untreated. Although environmental factors play a pivotal role in the causation of these diseases, identifying the genetics and physiological mechanisms can help patients who are predetermined for diabetes and prevent these complications from affecting the patient quality of life as the patient ages. It is also essential to start providing education on these conditions to make patients more aware on how to give themselves preventative treatment. Research has begun to identify several possible candidate genes that influence diabetes and its additional conditions; now, it is time to explore the variation of these genes and run genetic tests to identify the sole of the problem.

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