Candidate Genes/Proteomic Biomarkers of MOH

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Chronic headache is a topical problem of neurology, psychiatry and general practice. The medication-overuse headache (MOH) is one of the leading pathologies in the structure of chronic headache. The serum and urine proteomic biomarkers of MOH can potentially help with the identification of patients with MOH development.

Keywords: headache ; chronic headache ; proteomics ; proteogenomics ; serum biomarker ; urine biomarker

1. Introduction

Chronic pain (CP) is an essential problem in healthcare. Approximately 20% of the European population is affected by CP [1], which has a significant influence on their daily social and working lives. Moreover, the economic impact of CP is more than heart disease, cancer and diabetes put together [2]. It is worth mentioning that among chronic painful disorders, headaches are predominant. According to world literature, with an incidence of 3% per year, 4–5% of the general population suffers from chronic headache, known as headache occurrence ≥15 days per month [3][4][5]. Chronic forms of headache, such as chronic migraine or chronic tension-type headache, often involve a high and daily intake of combination analgesics and acute headache medications (AHMs), such as nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans [6]. Paradoxically, they only worsen the chronic symptoms, resulting in the development of the secondary headache, so-called medication-overuse headache (MOH) [7]. In the latest and current Third Edition of the International Classification of Headache Disorders (IHS ICHD-3), MOH, also known as a rebound headache, is described as a headache that is present on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication. Criterions of MOH: the overuse of simple analgesics on 15 or more days per month; or else the overuse of triptans, ergotamines, analgesics, opioids, and (caffeine or codeine-containing) combined analgesics on 10 or more days per month, for more than 3 consecutive months [8]. Although the prevalence of MOH in the general population is around 1–2% [9][10], MOH is still defined as a socio-economic burden worldwide, especially in lesser developed countries [11], associated with significant long-term morbidity, disability, and lower quality of life. According to systematic reviews of MOH epidemiology, it is most predominant in middle-aged women from 30 to 50 years old, with the male to female ratio around 1 to 3–4 [9][12][13][14][15]. The pathophysiological mechanisms of MOH development are still an ongoing debate. Nevertheless, frequent and regular consumption of acute headache medication does not seem enough to cause MOH, therefore individual predisposition and specifics of the medication class combined play a significant role in its development [16].

The proteomic analysis and the exploration of proteomic biomarkers are crucial in understanding a lot of medical conditions, especially cancer, cardiovascular and neurodegenerative diseases [17][18][19]. Thus, identification of chronic pain biomarkers can be helpful and valuable for clinicians in the diagnosis of patients at risk or with an already developed disorder, reducing the time and costs, selection of rational personalized pain treatment, and understanding of the underlying pathophysiological mechanisms of chronic pain development [20]. Moreover, a considerable number of patients with MOH can hide the truth from the doctor about the frequency and daily amount of acute headache medications they are consuming. Besides, the MOH phenotype is almost indistinguishable from other chronic headache phenotypes [11]. Therefore, it becomes even more challenging to diagnose MOH and selecting and monitoring the headache treatment. Furthermore, acute headache medication overuse leads to side effects, such as nephrotoxicity and kidney damage, gastrointestinal bleeding, liver impairment [11], especially in a group of patients who abuse NSAIDs [21]. It is not possible to prevent the development of renal impairment and acute renal failure caused by drug-induced nephrotoxicity by using traditional laboratory analyses, such as creatinine, creatinine clearance, urea, electrolytes, urine sediment [22]. However, urinary proteomics allows the potential risks of developing severe drug-induced kidney damage to be minimized by its detection in the early stages during a normal clinical presence, particularly in NSAIDs abusers, using a panel of protein biomarkers each informing on the integrated aspects of glomerular, tubular, and interstitial function [23].

The underlying mechanisms of chronic pain pathophysiology still remain poorly understood. Proteomics is one of the most promising areas that can significantly contribute to pain chronicity research, its better understanding and management.

2. Candidate Genes and Proteomic Biomarkers in Medication-Overuse Headache

2.1. Candidate Serum Proteomic Biomarkers of Patients with Medication-Overuse Headache

Candidate serum proteomic biomarkers of MOH are shown in **Table 1**.

Table 1. Candidate serum proteomic biomarkers of medication-overuse headache.

Protein Full Name	Entry Name	Gene Name	Locus	Protein Main Function	Theor. Mass.	References
Lipocalin-type prostaglandin D2 synthase	L-PGDS	PTGDS	9q34.3	Prostaglandin biosynthesis process	21,029	[23][24]
Apolipoprotein B100	APOB	APOB	2p24.1	Cholesterol metabolism	516,651	[23][24]
Alpha-2-macroglobulin	A2MG	A2M	12p13.31	Enzyme binding	164,613	[23][24]
Complement factor H	CFAH	CFH	1q31.3	Complement activation	143,480	[23][24]
Complement C3 (fragm)	CO3	C3	19p13.3	Complement activation	188,569	[23][24]
Hemopexin	HEMO	HPX	11p15.4	Metal ion binding	52,385	[23][24]
Serum albumin	ALBU	ALB	4q13.3	Metal binding	71,317	[23][24]
Alpha-1B-glycoprotein	AIBG	A1BG	19q13.43	Neutrophil, platelet degranulation	54,790	[23][24]
Complement component C9	CO9	C9	5p13.1	Complement activation	64,615	[23][24]
Kininogen-1	KNG1	KNG1	3q27.3	Cysteine-type endopeptidase inhibitor activity	72,996	[23][24]
Vitronectin	VTNC	VTN	17q11.2	Heparin binding	55,069	[23][24]
Haptoglobin	HPT	HP	16q22.2	Acute phase response	45,861	[23][24]
Apolipoprotein A-4	APOA4	APOA4	11q23.3	Lipid binding	45,371	[23][24]
Alpha-1-acid glycoprotein 1	A1AG1	ORM1	9q32	Inflammatory response	23,725	[23][24]
Serum paraoxonase/arylesterase 1	PON1	PON1	7q21.3	Hydrolase	39,877	[23][24]
Zinc-alpha-2-glycoprotein	ZA2G	AZGP1	7q22.1	Protein transmembrane transporter activity	34,465	[23][24]
Alpha-1-acid glycoprotein 2	A1AG2	ORM2	9q32	Acute phase response	23,873	[23][24]
Alpha-1-antitrypsin	A1AT	SERPINA1	14q32.13	Protease inhibitor	46,737	[23][24]
Immunoglobulin heavy constant alpha 1	IGHA1	IGHA1	14q32.33	Antigen binding	37,655	[23][24]
Retinol-binding protein	RETBP	RBP4	10q23.33	Retinol binding	23,010	[23][24]
Transthyretin	TTHY	TTR	18q12.1	Hormone binding	15,887	[23][24]
Apolipoprotein E	APOE	APOE	19q13.32	Lipid transport	36,154	[23][24]
Vitamin D-binding protein	VDBP	GC	4q13.3	Vitamin D transport	52,918	[23][24]

Protein entry name, according to the UniProtKB database. Theoretical molecular weight (Da).

2.2. Candidate Urine Proteomic Biomarkers of Patients with Medication-Overuse Headache

Candidate urine proteomic biomarkers of MOH are shown in **Table 2**.

Table 2. Candidate urine proteomic biomarkers of medication-overuse headache.

Protein Full Name	Entry Name	Gene Name	Locus	Protein Main Function	Theor. Mass.	References
Lipocalin-type prostaglandin D2 synthase	L-PGDS	PTGDS	9q34.3	Prostaglandin biosynthesis process	21,029	[23][24]
Uromodulin (or Tamm-Horsfall urinary glycoprotein)	UROM	UMOD	16p12.3	Cellular defense response	69,761	[21][23][24][25]
Alpha-1-microglobulin	AMBP	AMBP	9q32	Calcium channel inhibitor activity	38,999	[21][23][25]
Zinc-alpha-2-glycoprotein	ZAZG	AZGP1	7q22.1	Protein binding	34,259	[21]
Inter-alpha-trypsin heavy chain H4	ITIH4	ITIH4	3p21.1	Acute-phase response	103,357	[21][23][25]
Ig kappa chain C region	IGKC	IGKC	2p11.2	Complement activation	11,765	[21][23][25]
Non-secretory ribonuclease	RNAS2	RNASE2	14q11.2	Chemotaxis	18,354	[21]
Cystatin M	CYTM	CST6	11q13.1	Cystein-type endopeptidase inhibitor activity	16,511	[21]
Cystatin C	CYTC	CST3	20p11.21	Cystein-type endopeptidase inhibitor activity	15,799	[21][24][25]
Serum albumin	ALBU	ALB	4q13.3	Metal binding	69,367	[23][25]
Alpha-1-antitrypsin	A1AT	SERPINA1	14q32.13	Protease inhibitor	46,737	[23][25]
Actin, cytoplasmic 1	ACTB	ACTB	7p22.1	Cell junction assembly	41,737	[23][25]
Apolipoprotein H	APOH	APOH	17q24.2	Heparin binding	38,298	[23][25]
Serpin B3	SPB3	SERPINB3	18q21.33	Cystein-type endopeptidase inhibitor activity	44,565	[23][25]
Annexin A1	ANXA1	ANXA1	9q21.13	Calcium ion binding	38,714	[23][25]
Prostaglandin-H2-D-isomerase	PTGDS	PTGDS	9q34.3	Prostaglandin biosynthesis process	21,029	[23][24][25]
Perlecan (fragment)	PGBM	HSPG2	1p36.12	Angiogenesis	468,830	[23][25]
Transthyretin	TTHY	TTR	18q12.1	Protein binding	15,887	[23][25]
Proactivator polypeptide	SAP	PSAP	10q22.1	Enzyme activator activity	58,113	[23][25]
Nuclear transport factor 2	NTF2	NUTF2	16q22.1	Positive regulation of protein import into nucleus	14,478	[23][25]
Fatty acid-binding protein	FABP5	FABP5	8q21.13	Fatty acid binding	15,164	[23][25]
Beta-2-microglobulin	B2MG	B2M	15q21.1	Antigen processing and presentation of endogenous peptide antigen via MHC class I	13,715	[23][25]
Protein S100-A11	S10AB	S100A11	1q21.3	Calcium ion binding	11,740	[23][25]
Non-secretory ribonuclease	RNAS2	RNASE2	14q11.2	Chemotaxis	18,354	[23][25]
Protein S100-A8	S10A8	S100A8	1q21.3	Calcium ion binding	10,835	[23][25]

Protein entry name, according to the UniProtKB database. Theoretical molecular weight (Da).

The summary the Biomarkers of MOH are presented in **Figure 1**.

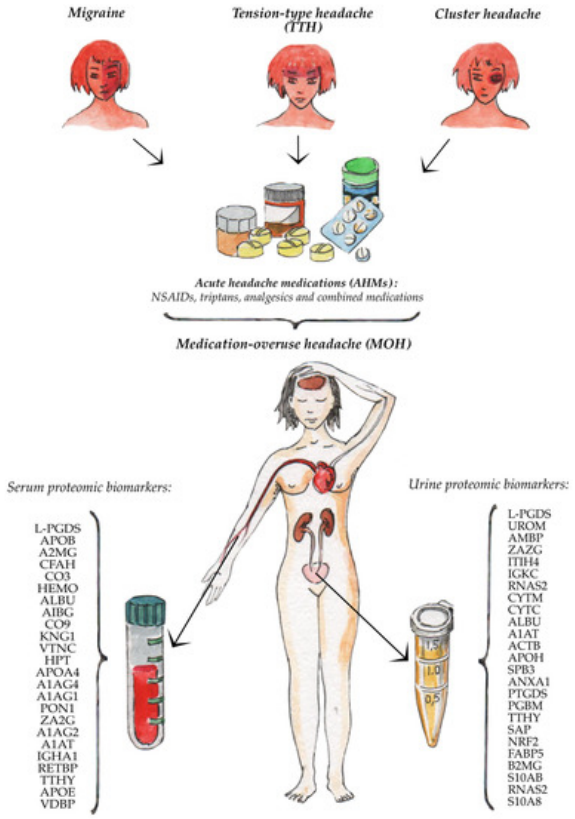

Figure 1. Serum and urine proteomic biomarkers of the medication-overuse headache.

3. Summary

L-PGDS is expressed in various tissues, such as the brain, retina, cochlea, and male reproductive organs, and it is found in different biological fluids, such as cerebrospinal fluid (CSF), ascites, seminal plasma, serum, urine, and amniotic fluid. Alongside hematopoietic-type PGDS (H-PGDS), L-PGDS is related to a group of prostaglandin D synthases (PGDS) responsible for converting PGH2 to PGD2 [26], which is involved in a variety of central nervous system (CNS) functions, such as sedation, nonrapid eye movement (NREM) sleep and PGD2-allodynia. In addition to synthesizing PGD2, a potent endogenous nociceptive modulator [27] within the cells, in the extracellular space and body fluids L-PGDS binds various small nonsubstrate lipophilic molecules such as retinal, retinoic acid [28], bilirubin, biliverdin [29], gangliosides [30], amyloid β peptides [31]. Therefore, L-PGDS can potentially be a promising proteomic biomarker as the entire prostaglandin system plays a huge role in pain and central sensitization development.

Vitamin D-binding protein (VDBP) is a monomeric glycoprotein synthesized and secreted predominantly by the liver. VDBP can be found in various body fluids, such as plasma, ascitic fluid, CSF. It was originally known as a group-specific component (GC) because of its worldwide polymorphisms [32]. It is also known as macrophage-activating factor (GcMAF/DBP-MAF) because it initiates macrophage activity, a key part of the host defense system [33]. VDBP has multiple functions, such as actin binding and neutrophil chemotaxis [34]. However, the main function of VDBP is to bind vitamin D and its plasma metabolites and transport them to target tissues. There are several studies showing the relation between Vitamin D deficiency or insufficiency and chronic headache development [35][36]. Possible mechanisms include the anti-inflammatory role of vitamin D, specifically, decreased production of inflammatory substances which activate trigeminal nerve, the main structure involved in migraine development [37][38]. Moreover, by inhibiting nitric oxide (NO) synthase expression, vitamin D reduces the production of NO, a key endogenous mediator in headaches, such as migraine [39] and tension-type headaches [40], deficient levels of VDBP in MOH patients can be associated with a decreased level of vitamin D, which can be one of the mechanisms of chronic headache development.

Apolipoprotein E (APOE) is a multifunctional protein which participates in lipid metabolism and carries lipids in different tissues of the body, including both the peripheral and the central nervous system [41]. APOE mediates the binding of APOE-containing lipoproteins and lipid complexes to specific cell-surface receptors, such as the low-density lipoprotein (LDL) receptors, the LDL receptor-related protein (LRP), the very low-density lipoproteins (VLDL) receptor, the APOE receptor-2, gp330. Moreover, APOE demonstrates genetic polymorphisms containing three common alleles, ε2, ε3, ε4 that encode three isoforms (APOE2, APOE3, APOE4) [42]. According to the available literature, NO synthesis is dependent on APOE polymorphisms. Thus, the APOE4 gene is involved in the production of NO through increased uptake of arginine in

the microglia compared to APOE3 gene [43]. APOE polymorphisms also influence the expression of cytokines which play a huge role in inflammation, pain modulation and central sensitization [44].

Alpha-1 antitrypsin (A1AT), also known as alpha-1 proteinase inhibitor, is an acute phase reactant and serine protease inhibitor (serpin) whose targets are elastase, plasmin, thrombin, trypsin, chymotrypsin, plasminogen activator, and is mostly produced in the liver and expressed by hepatocytes [45]. It is important to note that A1AT inhibits NO production [45], a key molecule in the pathophysiology of primary headaches [46].

Hemopexin (HEMO) is an acute-phase plasma glycoprotein with the highest affinity to heme among all known proteins and is responsible for transporting heme from the plasma to the liver for breakdown and iron recovery. Moreover, it has intracellular antioxidant activities and, therefore, is involved in protecting cells from scavenging and oxidative stress. HEMO is expressed in various tissues such as the nervous system, skeletal muscle, retina, kidney, but mainly in the liver [47]. HEMO was found at significantly different levels in the CSF of patients with leptomeningeal metastases of breast cancer with neurological complications [48] and with other neuropathologically confirmed diseases [49].

Haptoglobin (HPT) is an acute-phase protein whose main function is to bind hemoglobin (Hb) during hemolysis, forming the Hb-Hp complex, which is crucial for the elimination of free Hb by the macrophage CD163 scavenger receptor expressed on the liver Kupfer cells surface, therefore preventing kidney damage. HPT also acts as an antioxidant and plays a huge role in the neutralization of oxidative stress.

Retinol binding protein (RETBP) is specific carrier protein whose only known function is to transport retinol (vitamin A) from hepatic stores to target tissues [50].

Transthyretin (TTHY) is a homotetrameric protein mostly produced in the liver and choroid plexus of the brain. The main function of TTHY, the transport of thyroxine and RETBP, is well-known. However, other functions of this protein, namely in the nervous system, have emerged.

Urinary biomarkers are increasingly used in the diagnosis, classification and prognosis of kidney diseases. Uromodulin (UROM), also known as Tamm-Horsfall protein, is the most abundant protein in urine. It can also be found in serum in lower amounts. UROM is exclusively produced by renal epithelial cells in the kidney. Amongst all the functions of UROM, the most important ones are the regulation of ion transport in the thick ascending limb, immunomodulation and protection against urinary tract infections and kidney stones [51]. In clinical practice, UROM is used as a valuable biomarker of tubular damage and kidney diseases, including drug-induced nephrotoxicity caused by medication overuse.

Alpha-1-microglobulin (AMBP) is one of the urinary microproteins that are becoming more and more important in clinical diagnostics and practice. AMBP is a tubular glycoprotein, mostly expressed in liver, blood and kidney, which is used for detecting acute lesions of proximal tubules. It was first discovered 40 years ago in human urine [52]. Functions of AMBP are still unknown. However, some reports have suggested that AMBP may be involved in oxidant-scavenging and have enzymatic reductase properties as an antioxidant [53]. Altered plasma and urine levels of AMBP are usually markers of impaired liver or kidney functions. Therefore, nowadays, urinary AMBP is considered as a promising inexpensive alternative biomarker for the early detection and diagnosis of urinary tract disorders [54], including kidney damage, caused by acute headache medication overuse.

Zinc-alpha-2-glycoprotein (ZAZG) is a single-chain polypeptide secreted in various body fluids, such as serum and urine. Despite the fact that functions of ZAZG still remain unknown, some reports suggest that ZAZG has a lot of important functions in the human body, including fertilization and lipid mobilization, therefore it is considered as a multidisciplinary protein [55][56]. As its structural organization and folding characteristics are similar to the MHC class I antigen-presenting molecule, it may have a biological role in the immune response. ZAZG is used as a tumor biomarker for various carcinomas [56]. However, some immunohistochemical analyses have shown predominant expression in the kidney tubules of the human [57]. Therefore, urinary ZAZG may be a potential biomarker of renal damage, including drug-induced nephrotoxicity.

Inter-alpha-trypsin heavy chain H4 (ITIH4) is a liver-produced glycoprotein belonging to the liver-restricted serine protease inhibitor family. Its biological role is still unknown, as ITIH4 is cleaved in a number of different pathologies. However, it plays important role in various biological processes, such as inflammatory responses to trauma, liver formation or regeneration [58].

Immunoglobulin kappa constant (IGKC) is a constant region of immunoglobulin light chains, also known as antibodies, membrane-bound or secreted glycoproteins produced by B lymphocytes. The main function of IGKC is to serve as

receptors which, upon the binding of a specific antigen, trigger the clonal expansion and differentiation of B lymphocytes into immunoglobulin-secreting plasma cells. Secreted immunoglobulins play a significant role in the mediation of the effector phase of humoral immunity, which results in the elimination of bound antigens [59].

Nonsecretory ribonuclease (RNAS2) is a pyrimidine specific nuclease with a slight preference for cytotoxin and helminthotoxin. RNAS2 is selectively chemotactic for dendritic cells and possesses a wide variety of biological activities.

Cystatin C (CYTC) is a nonglycosylated basic protein encoded by the CST3 gene found in all nucleated cells. CYTC was first discovered in 1961 and formally named in 1984. CYTC is a potent inhibitor of lysosomal proteinases and extracellular inhibitors of cysteine proteases that play a huge role in human vascular pathophysiology [60]. Nowadays, CYCT is used as a more accurate alternative to serum creatinine for measuring glomerular filtration rate (GFR), one of the main parameters in the estimation of kidney function [61]. CYCT is increasingly used as an earlier biomarker for acute kidney injury, a superior marker of kidney transplant function, cardiovascular disease risk and transplant failure. Therefore, CYTC may be a promising proteomic biomarker for MOH and drug-induced nephrotoxicity, caused by acute headache medication overuse.

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