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MALE INFERTILITY: A REVIEW ON SPERMATOZOA PROTEOMICS AND FERTILITY-ASSOCIATED BIOMARKERS IDENTIFICATION

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ABSTRACT: Male infertility has remained a complex multi-factorial disease and needs advanced molecular studies. The development of effective diagnostic capabilities has resulted in the desire to create minimally invasive tests to help in the understanding of the etiology of male infertility. In recent times, research on human sperm proteomics has gained momentum and provides detailed information regarding spermatozoa's functional state. Sperm proteome changes are seen in many male infertility cases linked conditions. A Revolution in omics and the availability of advanced proteomic tools have increased the knowledge and understanding of the causes of male infertility. Proteomic tools and techniques including liquid chromatography, mass spectroscopy and MALDI-TOF are employed in sperm proteins profiling towards identifying the molecular pathways that are defective in infertile men. Proteomic information empowers better comprehension of sperm biochemistry and provides data that aids in improving reproductive outcomes in infertility patients. Therefore, this review explores the proteomic concepts and techniques for spermatozoa proteome analysis. It also examines the proteomic approaches, including the role of sperm proteomic data, in male infertility. We also give insights into the biomarkers employed in male infertility therapeutics and diagnosis. Identification of sperm proteins as biomarkers in diverse male infertility conditions may help the physician improve the management of this clinical condition.

INTRODUCTION: Up to 30% of men with normal semen parameters suffer from infertility, and the reason for this is unknown [1]. Infertility comes as an express term when there is no conception within 12 months of frequent unprotected sexual intercourse. In other words, it is referred to as the inability to conceive.

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Data from recent studies has revealed that infertility affects 15% of couples and has been grouped by the World Health Organization (WHO) as a disease of the reproductive system [2].

Impairment of male fertility is one of the major public health issues worldwide [3]. Globally, the World Health Organization has estimated that almost 190 million people are infertile. Alongside, male factors contribute to 50% of all cases of infertility worldwide [4]. Infertility is in two groups; primary and secondary infertility. This grouping is done on the basis of whether there is the presence or absence of previous successful pregnancies [5].

Primary infertility relates to couples with the inability to conceive after a minimum of 1 year of sexual intercourse without the use of contraceptive methods [6]. Secondary infertility, on the other hand, relates to couples who are unable to conceive after at least once, although not subsequently are known as secondary infertility. Primary infertility prevalence has been reported to be of a lower rate (1.5 – 2.6%) when compared to that of secondary infertility. Male factor has been linked to over 50% of all reported cases of infertility, although the reasons remain unknown [7]. One of the major steps in male infertility evaluation is basic semen analysis. This analysis encompasses both micro-scopic characteristics – sperm morphology, sperm concentration, progressive motility, total motility - as well as macroscopic characteristics – color, volume, viscosity, pH [8].

Although semen analysis still maintains its stand as the highpoint for evaluation of male fertility, yet it does not offer a systematic explanation for the subcellular changes. Since the standard semen analysis showed failure in predicting men's fertility potential, advanced sperm function tests, including terminal deoxynucleotidyl transferase UTP nick end labelling (TUNEL) assay or sperm chromatin structure assay (SCSA) measure seminal oxidative stress, sperm DNA fragmentation (SDF), have the potential of causing fertility failure. Regardless, these laboratory tests are still unable to explain the mechanisms at a subcellular spermatozoa level linked with male infertility [9]. Therefore, attention has shifted towards investigating the molecular factors linked with spermatozoa possibly affecting the process of fertilization adversely with a special searchlight beamed on the proteome of ejaculated spermatozoa [9, 10].

Proteomics and Spermatozoa: Human sperm proteomics research has gained increasing attention lately, which provides complete information about the functional state of the spermatozoa [11]. Proteomics encompasses the in-depth study of proteins with a focus on their specific functional and structural dimensions. From the proteomic point of view, recent studies conducted on spermatozoa have permitted the recognition of diverse proteins in spermatozoa responsible for the regulation of both defective and normal sperm functions. The proteome of seminal plasma provides profound information related to male reproductive health [12]. In proteomics research, the basic techniques extensively used target illumination of conformation, structure, purification, and measurement of sperm proteins concentration [13]. These proteomic techniques employed in sperm proteins structural analysis are electrophoresis and Mass Spectroscopy (MS), nuclear magnetic resonance spectroscopy, and X-ray crystallography [14].

Moreover, liquid chromatography and micro-fluidic separation techniques recently developed are extensively used for protein purification from spermatozoa or other samples. Additionally, chemical microarrays and western blot are employed for the determination of protein's density and concentration in sperm cells through the use of the corresponding antibody of the protein of interest. Also, diverse stains like silver stain and Coomassie brilliant blue stain are used for the identification of the individual protein positions within the gel, appearing as smudges or spots. Data obtained from the structural analysis can be for the identification of the responsibilities of diverse sperm proteins by comparing with similar sperm proteins with known functions. Generally, this process requires a large protein conformation and available functional databases [15, 16].

Bottom-up or shotgun proteomics is the commonest proteomic approach towards detecting >1000 proteins in a very short time period. The detection of sperm proteins is through the use of conventional and advanced proteomic techniques. The most popularly used technique for the separation of sperm proteins on the basis of the isoelectric focusing property and peptides' molecular weight is the two-dimensional (2D) gel electrophoresis. The combination of 2D-gel electrophoresis with MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) technique has been employed in the identification of 98 unique proteins in the human spermatozoa [17].

With reference to transcription, translation, and protein synthesis, mature spermatozoa go into a state of inactivity and hence, are very suitable for proteomic analysis. As a result, proteomics possesses the transformation potential towards understanding the working mechanisms of mature

sperm cells. Additionally, it is essential to hint that during fertilization, about half of a sperm cell's nuclear genetic material is what it contributes to the successive diploid offspring. Therefore, investigating the spermatozoa's genetic composition might as well offer helpful insights into congenital disorders.

Looking into proteomic data allows a better understanding of sperm biochemistry and gives information that assists in expanding the reproductive outcomes in infertility patients. Agarwal *et al.,* (2020) gave an example that mitochondrial proteome reflects the mitochondrial functionality that is directly synchronized with sperm motility in the nozoospermic patients as well as oxidative stress in infertile men with varicocele [18].

During the epididymal maturation of spermatozoa, it acquires its potential for fertilization prior to ejaculation. Both cellular (spermatozoa) and non-cellular (seminal plasma) components are found in the ejaculated semen. The seminal plasma is made up of secretions from testis, prostate, bulbourethral glands and seminal vesicles, that supplies protection and nourishment to spermatozoa [19, 20].

Sperm Proteomics: Introduction of advance proteomic platforms has made it easier to generate enormous amount of data in a short period of time [21]. Diverse studies have explored the global proteomic approach in sperm cells to explain the molecular mechanisms regulating male reproductive health. Sperm proteomics helps in understanding post-translational modifications, cellular pathways, and protein-protein interactions linked with normal gametogenesis, as well as the role of proteins in the fertilization process. Sperm proteomics enlightens the inherent operations of spermatozoa in infertile men, necessitating a deeper analysis and understanding of spermatogenesis at the molecular level.

Spermatogenesis is a complex process engaging hormonal coordination, over 2000 different genes as well the environmental factors.

The published work of Amaral *et al.,* (2014) showed that over 6,000 different sperm proteins are involved in a series of functional pathways, with the location of these proteins on the sperm linked to their site of origin in the epididymis and testis [22]. There has been the improvement of ease of protein identification, specificity, and sensitivity through the development of mass spectroscopy systems. This technique has the capacity to identify proteins within the seminal plasma, sperm membrane, and diverse sperm regions or mitochondria and probably the more essential protein-protein interaction networks. Understanding the importance of individual proteins working in diverse fertility processes alongside the way these proteins interact with each other is key. Also, studying the alterations in individual proteins gives insight into how they are affecting the downstream effect of their interaction and function, leading to diverse infertility phenotypes [23].

The use of animal models has revealed that elimination of several genes results in subfertility, alongside the desire to recognize an etiology of infertility which has propelled investigation into identifying the genes involved, epigenetic changes to these genes, the influence of these changes on infertility and subfertility, and biomarkers identification towards improving the diagnostic capability of semen parameters.

A recent study compared the proteome of the fertile men's ejaculate having high levels of ROS to that of fertile men having normal levels of ROS. The study revealed that many antioxidant proteins were present in higher levels in men have increased levels of ROS. This suggests that certain specific proteins are available, which may be upregulated in fertile men having high levels of ROS and acting protectively to control ROS negative effects and fertility preservation [24]. In addition, heat shock protein A4L has been found to be deregulated in sperm in patients having as thenozoospermia, leading to reduced sperm motility and penetration of sperm-oocyte [25]. This represents a small fraction of diverse studies with promising results targeting particular proteins appearing to be located in the seminal plasma and sperm that might be used as biomarkers for male infertility in the future. A proteomic study was conducted by Borrachina and collaborators on the seminal plasma of infertile patients having azoospermia, normozoospermic, oligoasthenozoospermia, and asthenozoospermia [26]. The findings and conclusion from the study were that the present classification of infertile patients on

the basis of altered semen parameters led to high heterogeneity in the seminal plasma proteomic profile. Through the utilization of proteomics and bioinformatics analysis, the suggestion has been that MME (membrane metalloendopeptidase) and family with sequence similarity along 3 (FAM3D) with levels of ROS in the seminal plasma can be used as good markers for male infertility diagnosis [26]. Seminal plasma proteomic study in idiopathic oligoasthenozoospermic men showed differential protein expression like lipocalin-1 or galectin-3-binding protein (M2BP), glycosylated epididymalsecretory protein E1(NPC2), which gives a framework for advanced investigations of mechanisms underlying oligoasthenozoospermia [27]. Although these studies did not give any evidence on the seminal plasma proteomics on the basis of infertility type, yet they provided relevant information on mechanisms linked with male infertility [28].

Aside from the fact that there some other studies that tried to engage sperm plasma membrane characterization, spermatozoa-specific processes like capacitation and calcium-binding ability also offer relevant information on human fertility as well as animal species [29]. Regardless of the fact that it's been beyond 15 years now that tyrosine phosphorylation was recognized as an indicator of capacitation alongside its ability to play an important role in fertilization, proteins role as well as that of their respective sequence of activation continues to be a mystery. Till date, only a small fraction of individual proteins have been identified for this essential fertilization event. Studies have shown that the phospholipid hydroperoxide glutathione peroxidase in spermatozoa of hamster during tyrosine phosphorylation come capacitation [30]. Regardless, revealing the entire picture of the physiology of human sperm is still far-fetched, particularly from proteomics' viewpoint.

Spermatozoa are believed in the modern world to be providing a potential study source for the investigation of diverse, impressive findings generally controlling reproduction. Proteomics stands as an outstanding tool for the evaluation of the molecular mechanisms regulating the functions of sperms, for giving a clearer perspective on how we understand male fertility and infertility, as well as for the characterization of the state of complete contraception [27]. The consideration on spermatozoa is that it helps in addressing spermatozoa posttranslational modifications and also for elucidating the molecular basis for defective functions of sperms with effects on our capacity for diagnosis and treatment of male infertility. Hence, the proteins identified should be extensively examined for the determination of already existing clinical value for the evaluation of fertility/infertility [18]. Concurrently, there should be the consideration of factors that can affect proteomics, and they must be put into consideration during the translation of discoveries from proteomics. Diversesperm proteins databases are now taking their roles as essential knowledge sources. Protein catalogs emanating from proteomic approaches are of high value because they represent protein groups that can be exposed in a specific pathological/physiological condition. Certain proteins also display diverse functions, playing diverse roles in the entire organism. The molecular mechanisms linked with the functions of sperms such as capacitation, fertilization (sperm-oocyte interaction), motility, and acrosomal reaction have been noted to be altered in the spermatozoa of IVF failure patients with normozoospermic semen parameters.

There is an existing link between deregulated proteins and protein transport, cell growth and/or maintenance, protein metabolism, sexual reproduction, and metabolic process. Additionally, there has been a report of proteins involved in chromatin assembly to be defective in spermatozoa from normozoospermic infertile men with failed IVF. Sperm dysfunction (sperm-oocyte inter-actions, motility, and capacitation) and defective spermatogenesis are seen as the main cause of failed fertilization leading to male infertility. Proteomic profile of immature and mature spermatozoa revealed that the exportin, importin as well as other ras-related proteins are sperm homeostasis markers during the process of spermatogenesis [31]. Sperm DNA integrity is regulated by the expression and abundance of sperm proteins. The functions of the molecular pathways like the prostaglandin biosynthesis and fatty acid-binding were reported to be rich in spermatozoa having damaged DNA [32]. CRISPLD1 (Cysteine-rich secretory protein LCCL domain-containing 1), RARRES1 (retinoic acid receptor

responder protein 1), CRISPLD2 (cysteine-rich secretory protein LCCL domain-containing 2) were proposed as low SDF biomarkers, while for high SDF biomarker, proteome subunit alpha type-5 protein has been considered as being a potential seminal biomarker. Diverse studies have shown that sperm proteins working in degradation pathways and protein folding are deregulated in male infertility conditions. Dias *et al.,* recently submitted that the mechanism of misfolded protein degradation is affected in seminoma patients, and HSPA2 protein was proposed as a marker of infertility in men having Tuberculosis [33].

TABLE 1: PROTEOMIC STUDIES ON HUMAN SPERMATOZOA TO ACCESS MALE FERTILITY.

Proteomic Technique	Study findings	Author
MALDI-TOF	131 proteins identified as 2D reference map provider of mature human sperm spermatozoa	Mart´ınez-Heredia *et al.* [17]
LC-MS	35 proteins identified as sperm immunogenic antigens	Domagala *et al.*[34]
MALDI-MS	Creation of a 2D human sperm proteins map with high resolution through the 16 proteins identified in the study	Li *et al.* (2007) [35]
LC-MS/MS	1760 proteins identified to be composed of human sperm	Johnson *et al.*[36]
MALDI-TOF	101 spots identified from infertile patients	De Mateo *et al.*[37]
MALDI-MS	18 proteins identified – sperm membrane antigens	Bohring *et al.*[38]
MS/MS	240 S-nitrosylated proteins identified to be addressing Capacitation induced by nitric oxide	Lefievre *et al.* [39]
MALDI-TOF	10 separately expressed proteins identified in asthenozoospermic patients compared with those of normozoospermic donors	Zhao *et al.*[40]
LC-MS/MS	1056 gene products identified from human sperm populations	Baker *et al.*[41]

Diagnostic Biomarkers in Male Infertility: A measurable or quantifiable biological parameter serving as an index for some states of disease is referred to as a biomarker. Cost-effectiveness, accuracy, minimal invasiveness, ability to detect early-stage disease are the properties of an ideal biomarker [42]. Gene expression does not necessarily translate into protein expression, and the protein complement varies from cell to cell [6]. This makes proteomic analysis an attractive target for biomarker development.

For male infertility in the field of fertility, SA acts as the basic biomarker. Regardless, SA still is an imperfect test since it may be affected by physiologic parameters such as systemic illness, abstinence interval, environmental exposures, lifestyle factors inclusive of activity and diet, and medical comorbidities [43].

Considering the high semen parameters variability, there has been the development of multiple adjunct biomarkers, including acrosome reaction testing, DNA damage testing, anti-sperm antibody testing, sperm-zona pellucida binding tests, sperm penetration assays, and hyaluronan binding assays. One of the extensively used biomarkers in the infertility field is the ASA (Antisperm antibody) testing. ASAs have been seen in over 12% of infertile men when compared to 2.5% of fertile men. Numerous studies on ASA effects on semen parameters have shown opposing results, although ASAs have been perceived to exert a negative impact on fertility by impacting sperm quality [44]. Cui *et al.,* conducted a meta-analysis that suggested that ASA may have a negative effect on progressive motility and sperm concentration [45].

As at the time when ICSI was fondly used, functional sperm tests have been relinquished as the functional aspects of the sperm that can be bypassed with direct intracytoplasmic injection. Regardless, these tests have retained some utility since they may permit the provider to direct a patient away from futile IVF or IUI rounds in some circumstances [46]. There has been an increased number of reports in recent years on seminal plasma proteome towards identifying potential biomarkers for diverse conditions and pathologies linked to infertility. Sperm proteomic studies have shown that biomarkers assist in male fertility potential evaluation towards differentiating between diverse infertility etiologies and helping to make predictions of the outcomes of ART [47].

The introduction of these biomarkers in clinical establishments will aid the transformation of the therapeutic and diagnostic field of male infertility. DEPs have been shown to be potential biomarkers for the same pathology by different studies.

Differences in the study of specific inclusion /exclusion criteria, methods of sample preparation, as well as proteomic analysis techniques used could be the reasons for this finding. Although the presently available proteomic techniques are of high sensitivity and efficiency, their utilization in clinical setup for fertility management needs more investigation. This is major due to the inclusion of sophisticated and costly instruments requiring skilled and well-trained technicians. An extensive application of proteomics towards understanding male infertility may be engaged through the introduction of new easy to operate and cost-effective devices.

Numerous genes are playing diverse roles in spermatogenesis. With the emergence of whole-genome assessments through the use of CGH (comparative genomic hybridization), next-generation sequencing or high-throughput sequencing technologies, as well as analysis of SNP (single nucleotide polymorphism) arrays, studying a large quantity of genetic material towards discovering certain abnormalities impacting infertility is becoming possible. These technologies are promising with respect to affordability and effectiveness in the identification of potential biomarkers and candidate genes in male infertility. There is an ongoing investigation on other spermatogenesis metabolic products as biomarkers for male infertility. Zhao *et al.*, used GC-MS for the identification of sperm metabolites linked with idiopathic as then ozoospermia. Quite a number of metabolites were identified in this study, of which they were either down-regulated or upregulated, involved in energy, nucleoside metabolism, and amino acid [48]. The work of Krausz and Riera-Escamilla gave comprehensive insights into these techniques, explained their utility, as well as the series of genes responsible in male infertility [49]. Exploring biomarkers and epigenetic changes may lead to additional treatment and screening options in the future [50].

CONCLUSION: Over the years, male infertility has maintained its stand as a complex disease encompassing the activities of numerous genes and proteins. Studying these factors alongside their epigenetic changes to sperm DNA continues to be an appealing target for specific biomarkers development having the ability to recognize the etiology of male infertility in a minimally invasive fashion. Although many factors are causing infertility, the development of biomarkers in line with infertility phenotypes is still elusive. With our increased understanding of the factors involved, we have the possibility of implementing our knowledge of these factors into the process of clinical decision-making.

Furthermore, although the analysis of proteomic profiles of semen and sperm maintains its attractive nature in a minimally invasive way towards diagnosing male infertility with the potential of distinguishing infertility phenotypes, there is still a limitation in the clinical application of these profile panels partly as a result of an extensive range of proteins, metabolites, and peptides observed in semen samples for which they can be affected by diverse environmental factors to varying degrees between individuals. Essentially, more research is needed before using these profile panels for large-scale clinical implementation.

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