Universitat de les Illes Balears

BACHELOR'S THESIS

DIETARY COMPONENTS AND THEIR EFFECTS ON HUMAN SPERM QUALITY – A MOLECULAR APPROACH

Anna Rosaria Munch

Degree in Biology

Faculty of Science

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Key words:

Sperm quality, SDF, oxidative stress, diet, ROS, antioxidants, DNA, fatty acids, sRNA, tRNA.

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Index

Abbreviations

ACAT	Acetyl Coenzyme A
ATP	Adenosine Triphosphate
ALA	α-Linolenic Acid
CAT	Catalase
DDT	Dichlorodiphenyltrichloroethane
DNA	Deoxyribonucleic Acid
DHA	Docosahexaenoic Acid
EDC	Endocrine Disrupting Chemicals
EPA	Eicosapentaenoic Acid
ERC	Excess of Residual Cytoplasm
GGNBP1	Gametogenetin Binding Protein 1
Gly	Glycine
GPx	Glutathione Peroxidase
GTP	Guanosine Triphosphate
HFD	High Fat Diet
H_2O_2	Hydrogen Peroxide
IM	Immotility
KO	Knock-Out
LAC	L-Acetyl Carnitine
LC	L-Carnitine
MedDiet	Mediterranean Diet
mRNA	Messenger Ribonucleic Acid
MUFA	Monounsaturated Fatty Acid
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
NCBI	National Center for Biotechnology Information
ncRNA	Non-coding Ribonucleic Acid
NLM	United States National Library of Medicine
NO·	Nitric Oxide
NP	Non-progressive motility
OH·	Hydroxyl Radical Anion
$ONOO^-$	Peroxynitrite Radical
O_2^-	Superoxide Radical Anion
$^1O_2$	Singlet Oxygen
PR	Progressive motility
PUFA	Polyunsaturated Fatty Acid
QA	Quality Assurance
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SAM	S-adenosylmethionine
SDF	Sperm DNA Fragmentation
Se	Selenium
SOD	Superoxide Dismutase
sRNA	Small Ribonucleic Acid
SSB	Sugar-sweetened Beverage
TP	Transition Protein
tRF	Transfer Ribonucleic Acid Fragment
TRH	Thyrotropin Hormone
tRNA	Transfer Ribonucleic Acid
tsRNA	Sperm Transfer Ribonucleic Acid
WHO	World Health Organization
Zn	Zinc

Summary

In the last decades, cases of male infertility have been related to different external factors such as alcohol intake, smoking, different chemical compounds or the administration of certain drugs. More recent research revealed that also the diet and its components might have contributed to the observed increase in male infertility, specifically, through its effect on sperm quality. A lot of studies focusing on this relationship are purely epidemiological, although a growing understanding of the molecular mechanisms involved in the formation, development and maturation of sperm is available. The objective of this bachelor thesis is to clarify the molecular mechanism that might be involved in the effect of different diets and its dietary components on sperm quality. In order to carry out this bachelor thesis PubMed has been the main information source used. As a result, several possible mechanisms how dietary components may modulate sperm quality parameters could be identified. In this context, red or processed meat is able to affect sRNA and tRNA involved in the sperm maturation process leading to a reduction in sperm number, whereas the evaluation of seafood, another source of protein, is a complex task as this food, in general, has a positive influence on sperm count, but this effect may be overcompensated depending on the amount of its main contaminant methyl mercury. An insufficient supplementation of certain vitamins, in particular C and E, but also trace elements (zinc and selenium) increases the number of reactive oxygen species, to which spermatozoa are especially sensitive, leading to nucleotide modifications, strand break of the DNA and chromatin cross-linking. The mentioned trace elements may also play a role in male reproductive epigenetics by acting on enzymes adding or removing epigenetic marks of the germ cells during spermatogenesis. Consequently, some diets, for example the Mediterranean Diet, have to be considered more beneficial to maintain the quality of the sperm than others, for example the Western Diet.

Introduction

The development of those cells that will later on produce spermatozoa begins already in the yolk sac during embryonic development, where about 100 primordial germ cells are formed. Around the fourth week after fertilization these cells migrate to the developing gonads of the male reproductive organ and meanwhile they increase their number through mitotic proliferation. Although differentiation of the primordial germ cells starts early, the production of functional spermatozoa (spermatogenesis) does not start until puberty when the testicles become fully developed (De Jonge & Barratt, 2006).

Spermatogenesis is a complex process, which continues during male's lifetime and implies episodes of cell migration, mitotic and meiotic cell division as well as a differentiation and maturation process. In order to carry out the fertilization and the embryonic development it is very important, that all these episodes take place in a correct order, and with no mistakes. If an error occurs during the developmental course, production of fully functional sperm may be inhibited leading to male infertility. This pathophysiological clinical state can be classified into different degrees of severity that depend on the time when spermatogenesis fails. Very early problems, which occur already during fetal development, will lead to a more serious infertility than an error taking place in later stages of spermatogenesis (De Jonge & Barratt, 2006). Infertility affects about 7% of all men (Krausz, 2011) and in the past decades, different studies have found evidence that sperm quality in general has been decreasing and is paralleled by an increasing number of cases of infertility (Zegers-Hochschild et al., 2009).

The quality of the seminal fluid, another term for sperm quality, is a determining factor in achieving a successful fertilization. According to the *Laboratory manual for the Examination and processing of human semen* published by the World Health Organization (WHO) some parameters have to be taken into account to establish a standardized and accurate indication of a male's fertility status. For example, sperm volume should be in the range of 1.5 – 2 mL, sperm concentration in the range of 15 - 20 million/mL, dynamic motility between 32 and 50% and normal spermatozoa forms between 4–14%. All these values have been declining in recent years (Garrido & Rivera, 2017).

This deterioration of sperm quality and the increasing incidence of male infertility have been related to various factors such as the intake of certain pharmaceutical drugs, environmental toxins, cigarette smoking, alcohol consumption and also specific diet habits.
In fact, several drugs pertaining to different pharmacological classes can influence male's fertility due to various molecular mechanisms sometimes also implying hormonal effects. These pharmacological classes include analgesics, α-blockers, antiandrogenic drugs, hormonal treatments and diuretics, which all may directly or indirectly affect the spermatogenesis or cause sexual dysfunction, which implicates a difficulty in individuals to experience a normal sexual activity including physical pleasure and orgasms. Importantly, some effects can be reverted by stopping the drug usage, whereas others are permanent (Semet et al., 2017; Brezina et al., 2012).

In the environment, different chemicals used in agriculture can affect testicles and sexual hormones, thus ascending the infertility rate (Jenardhanan et al., 2016). In particular, exposure to Endocrine Disrupting Chemicals (EDC) in high concentrations is able to cause

harmful effects on the physiology of the reproductive system (Krieg et al., 2016). In addition, some researchers point out that exposure to pesticides like Dichlorodiphenyltrichloroethane (DDT) or certain heavy metals, may be causing oxidative stress thereby deteriorating sperm quality or sperm apoptosis (Pant et al., 2014; Carette et al., 2013). Regarding air pollution, some evidence has been found that some pollutants do have an effect on semen quality parameters such as the spermatozoa morphology or unbalancing the X-Y chromosome ratio (Lafuente et al., 2016; Radwan et al., 2018). Indeed, laptops have been noticed to produce scrotal hyperthermia and, as a result, to affect spermatogenesis (Sheynkin et al., 2005).

Addiction-related life-style habits, like cigarette smoking and increased alcohol consumption, are related to alter several seminal parameters and have the potential to reduce overall seminal quality compared to non-smokers and non-alcoholic men (Martini et al., 2004). However, the specific pathophysiological effects of both habits are no identical. Cigarettes have been linked to an inferior semen volume and a total decreasing sperm count leading to an anomalous semen quality (Tang et al., 2019). In contrast, occasional alcohol drinking seems not to affect semen parameters (Jensen et al., 2014), while a daily alcohol intake is associated to altered sperm morphology and the level of sexual hormones (Anifandis et al., 2014; Muthusami et al., 2005).

The ingestion of alcohol as beverage accompanying meals, has led other researchers to study also the effect of non-alcoholic but sugar-sweetened beverages on sperm quality, pointing out a negative effect of these on sperm motility (Chiu et al., 2014). Contrarily, it has been evidenced that some dietary components of the Mediterranean Diet may actually improve sperm quality (Afeiche et al., 2014; Braga et al., 2012; Vujkovic et al., 2009), whereas other dietary products, such as ultra-processed food, may impact in a negative way on the parameters of sperm quality (Afeiche et al., 2014; Eslamian et al., 2016).

Hypothesis

In the last decades, infertility rate has been constantly increasing leading to the implementation of assisted reproduction techniques in order to overcome the lowered birth rates. Infertility may be caused by many different factors, but there is a growing body of evidence indicating that an important variable could be the composition of the modern Western diet. In this context, different food components may also have different effects on the quality of spermatozoa and are probably caused by different molecular mechanisms related to the male reproductive system.

Objective

To determine the molecular mechanisms by which different dietary components influence on human sperm quality parameters.

Materials and Methods

The bibliographic research has been carried out by using, in first place, the database PubMed (Public Medline) and, to a lesser degree, the databases Science Direct and Google Scholar. These databases have been chosen as a scientific source of information to cover the main subject in this bachelor thesis due to the great variety of articles they provide.

The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the MEDLINE database, which includes more than 30 million references and abstracts of peer-reviewed biomedical publications, journals of life science and online books. PubMed, provided by the National Center for Biotechnology Information (NCBI), has access to this information and makes it available through a public website free of charge (Hunter & Cohen, 2006).

As the topic of this bachelor thesis is closely related to health sciences and PubMed is mainly focused on the biomedical field, it has been the most consulted database to find publications for this work. Although some articles were only fully accessible after purchase, clicking on the full text links that allowed downloading the article with the usage of the university credentials could solve this issue. In other cases the work was published in an open-access format and the option to download it free of charge was available for everyone.

The search for manuscripts started with a general approach, where the keyword <*sperm*> was searched in conjunction with other words such as <*smoking*>, <alcohol intake> or <medication impacts> in order to find results that showed, if the quality of the sperm was affected. The next step was to look for a relationship between two or more possible factors that influenced sperm quality, such as the combined intake of alcohol and tobacco. On the other hand, a rigorous search of the effect of different types of diet on sperm quality and on the parameters that define sperm quality has been carried out, differentiating between healthy food included in the Mediterranean diet and those components considered harmful, if administered in inadequate quantities or after being ultra-processed.

In detail, the bibliographic search has been conducted by using different keywords separately, a combination of keywords by adding a plus sign, and the usage of double quotes in the search field (Table 1). Articles with promising titles, that were found in the bibliographic section of publications with high relevance, were also considered during the ongoing search.

Search field	
Male + infertility	“Male infertility”
Epigenetics + sperm	Spermatozoa
Oxidative stress + Sperm + Diet	Sperm + Cell
“Sperm epigenetics” + Diet	“Sperm quality”
“Sperm quality” + Diet	Diet + Sperm
Alcohol intake + sperm quality	Smoking + sperm quality
Cigarettes + sperm	Cigarettes + sperm + alcohol
Male Reproductive Health	Environment + sperm
Sperm DNA Fragmentation + sperm quality	Chemicals + sperm quality
Drugs + Infertility	“Dietary patterns” + male fertility
RNA + sperm	Semen quality parameters

Table 1. List of keywords used in the consulted database for acquiring the information presented in this bachelor thesis.

The search results obtained in the database appeared chronologically in the output window and in a way that it made possible to read the abstract of each article in order to decide whether it could be useful or not. Once the abstracts and the articles were read and selected because of their interest for the bachelor thesis, they were downloaded and an introductory first reading was carried out to then decide definitively, if the article provided sufficiently relevant information for the topic. Regarding the research subjects, no age group discrimination has been made to consider the articles valid for the bachelor thesis.

Finally, in order to carry out the writing of the thesis, several articles and resources have been used, which can be found in the references section. The quotes included in this thesis are original references. Other articles have also been consulted that have not been included in the bibliography but have served for a better general understanding of different concepts and to broaden the personal knowledge of the topic.

Results and Discussion

In the testes located in the male reproductive system, the seminiferous tubules are found. The wall of these structures is made up of several layers of cells known as the germinative epithelium or seminiferous epithelium (Fig. 1). Also, this epithelium is made up of cells called Sertoli cells and other cells that are part of the spermatogenic process; the spermatogenic lineage. These last ones are in charge of producing sperm. In the first instance, some cells of the spermatogenic lineage known as germ cells migrate from the yolk sac of the embryo to the gonads that are currently developing. It is in this moment that these cells proliferate and colonize the gonads, which leads to the formation of cells called spermatogonia that will start the spermatogenesis process.

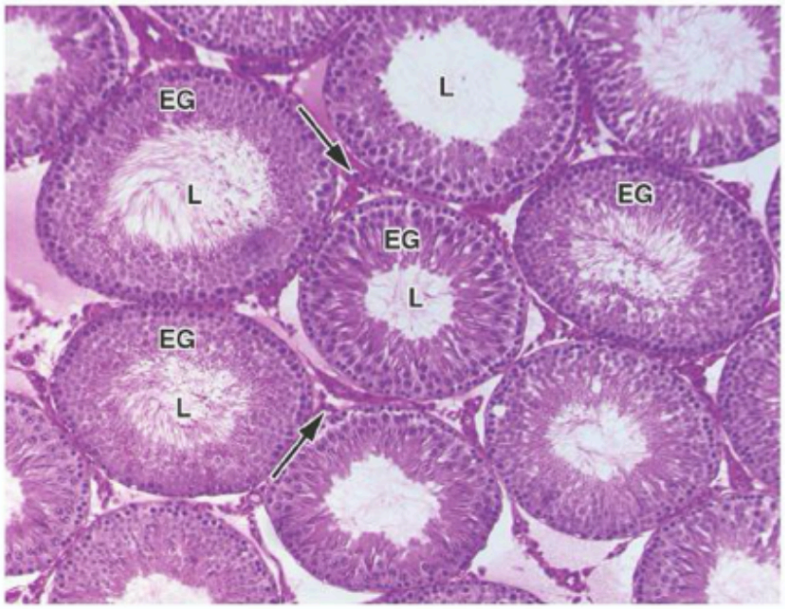

Figure 1. Presence of seminiferous tubules in the testicle. EG = Germinative Epithelium; L = Light of the tubule. Image from Junqueira & Carneiro, 2015.

The ultimate goal of spermatogenesis is the formation of sperm. During this process, the spermatogonia are located near the basal lamina of the seminiferous epithelium. It is during the puberty stage of man, when meiotic division processes begin to occur in spermatogonia, where daughter cells will be produced and that can follow two different paths; some can be kept as stem cells of other spermatogonia, while other cells can continue their division (type A spermatogonia) or differentiate during more cycles of meiotic division in order to give rise to type B spermatogonia. At the histological level, it is difficult to differentiate both types of spermatogonia, but in any case, those of type B will give rise after several divisions to the primary spermatocytes. These spermatocytes and their descendants are held together by bridges made of cytoplasm until the end of spermatogenesis is reached. Primary spermatocytes are the majority of cells of spermatogenesis that are capable of duplicating their DNA, which means that they have 46 chromosomes, that is, twice as much DNA as a

normal diploid cell (somatic cell) in the body. During the anaphase of the first meiotic division, the homologous chromosomes separate. And from this division of a primary spermatocyte, two secondary spermatocytes with a complement of 23 chromosomes and the usual amount of DNA from a diploid cell arise. These secondary spermatocytes then enter the second meiotic division to originate two cells called spermatids, each with 23 chromosomes and half the amount of normal DNA (these are haploid cells).

Once these spermatids are produced, the process of spermiogenesis begins, which is the final phase of sperm formation. During this complex process, cell divisions do not occur, but there is the formation of a structure known as the acrosome as well as the condensation and lengthening of the nucleus. There is also the formation of the flagellum and the loss of most of the cytoplasm. The result of spermiogenesis is, then, the formation of mature sperm, which is released in the light of the seminiferous tubule (Fig. 2).

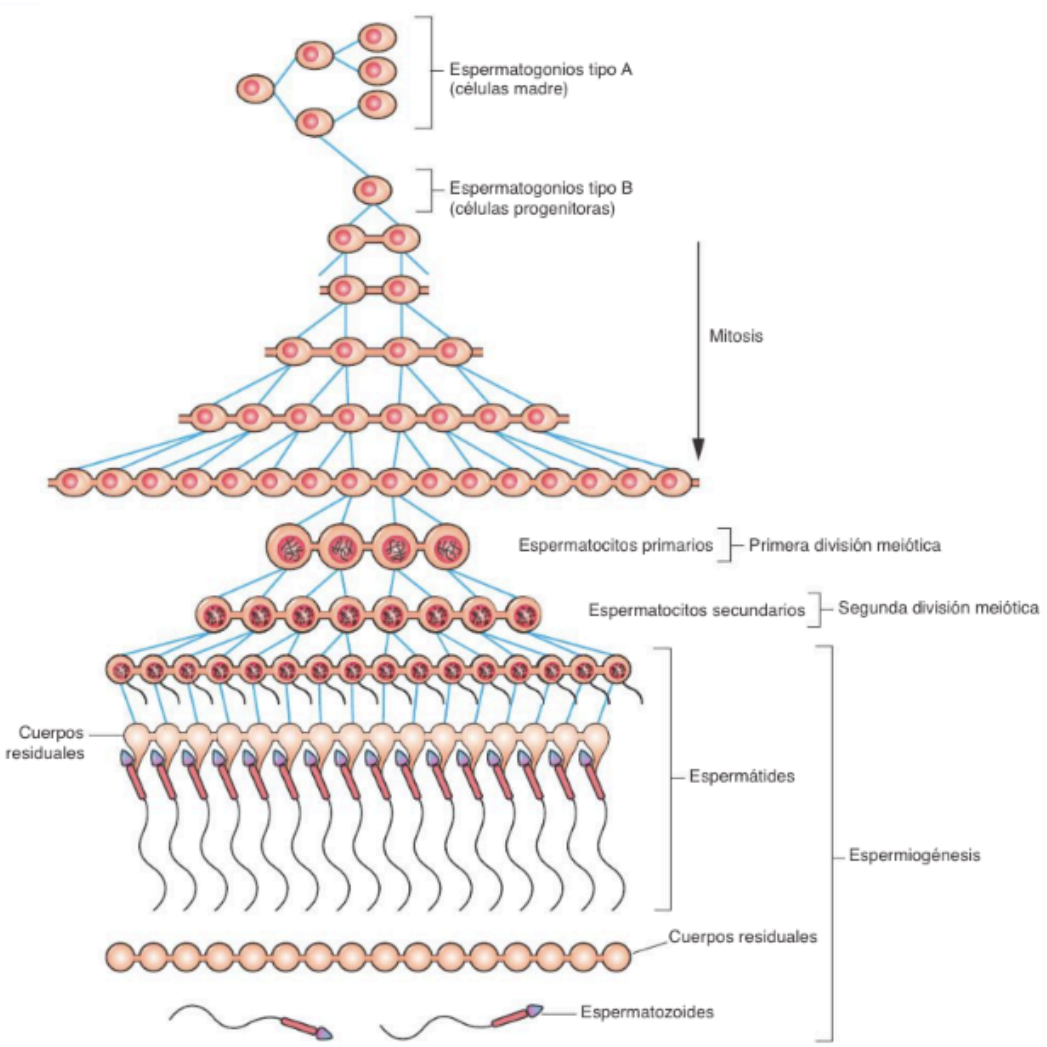

Figure 2. Diagram of the spermatogenesis and spermiogenesis process. Image from Junqueira & Carneiro, 2015.

Spermiogenesis comprises three stages: the stage of the Golgi complex in which, from the union of proacrosomal granules, a single acrosomal granule is formed inside a vesicle called acrosomal vesicle. This formation is followed by the migration of the centrioles towards the surface of the cell and on the opposite side of the acrosomal vesicle, to begin the formation of the axoneme (set of microtubules that form the central axis of a flagellum). In the second stage, called the acrosome stage, the acrosomal vesicle and the acrosomal granule extend over the nucleus to form, first, the acrosomal cap and then, finally, the acrosome. This structure contains different types of enzymes and does work in a very similar way to a lysosome. It is thanks to this acrosome that fertilization is possible by dissociating the cells that form the radiated crown and the zona pellucida of the female oocyte.

The moment when a sperm finds an oocyte, the outer membrane of the acrosome fuses with the spermatozoan cytoplasmic membrane, releasing a series of enzymes from the acrosome to the extracellular space in order to fertilize the oocyte. This first step of fertilization is known as the acrosomal reaction, and changes that may occur in it are associated with male infertility.

On the other hand, the flagellum is formed from one of the centrioles and the mitochondria accumulate in the proximal part of the flagellum, in the so-called intermediate piece of the sperm. The characteristic disposition of the mitochondria is related to the movement of the sperm and with a high energy consumption. Furthermore, flagellar movement is associated with the interaction between microtubules, dynein protein (with GTPase activity) and ATP. During the final stage of spermiogenesis, the nucleus lengthens and condenses in an opposite orientation to that of the flagellum. Then, in the maturation stage, a large part of the cytoplasm of the spermatids is removed, forming the residual bodies that will be phagocytized by the Sertoli cells and, thus, the mature sperm can be released into the light of the seminiferous tubule (Fig. 3). The released mature sperm cells reach the epididymis, where they are stored in a particular fluid known as testicular fluid, that contains steroids, proteins and ions produced as well by the Sertoli cells and with the contribution of the accessory sexual glands like the seminal vesicles, the prostate and the Cowper glands. Finally, the mature sperm is released during ejaculation (Junqueira & Carneiro, 2015).

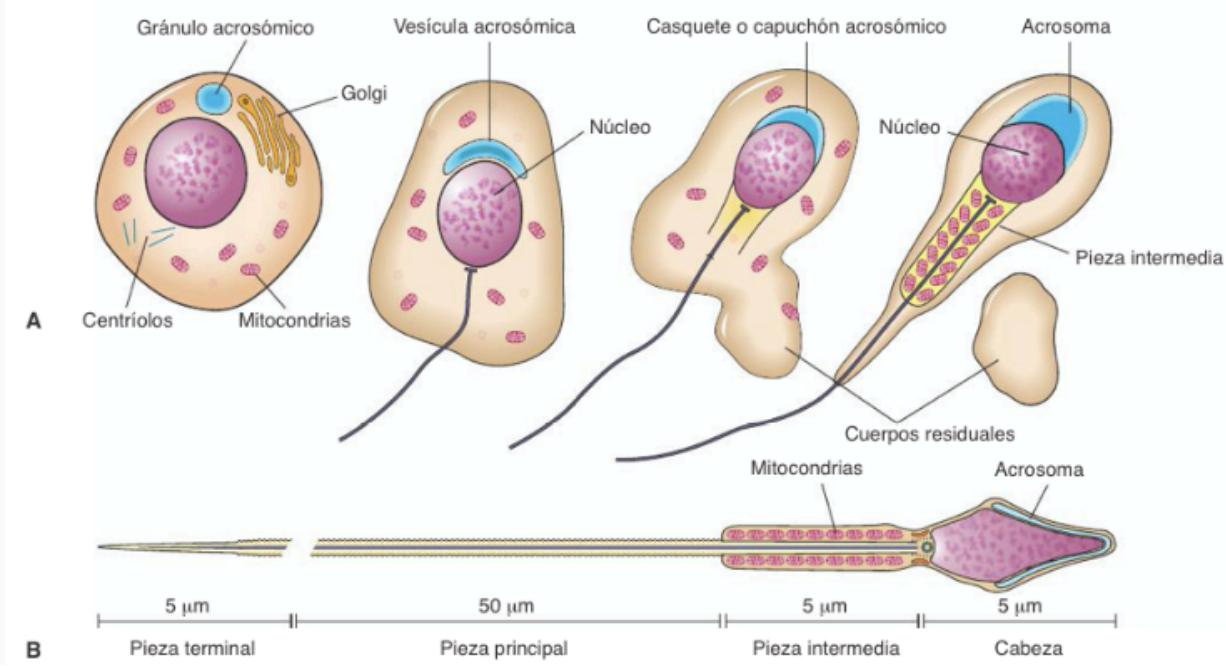

Figure 3. Main changes from spermatids to sperm formation during spermiogenesis. Image from Junqueira & Carneiro, 2015.

Two quantifiable parameters are mainly taken into account when it comes to analyze semen samples: the quantity or total number of sperm cells and the volume of the total fluid produced. However, the vitality, morphology, motility of the sperm cells as well as the composition of the seminal fluid also contribute to the proper functioning of the sperm and therefore have to be considered. Therefore, in order to determine male infertility, it is necessary to assess and take into account certain parameters that are quantified through a semen analysis, which provides additional essential information (WHO, 2010).

Sperm Quality Parameters

According to the *Laboratory manual for the Examination and processing of human semen* published by the World Health Organization (WHO), who has been the first to attempt and standardize semen variables based on evidence, focuses in the following parameters:

Sperm motility: it has a three-category division and should be calculated in percentage.

- Progressive motility (PR): spermatozoa moving in an active way in circles or linearly.
- Non-progressive motility (NP): other moving patterns with an absence of progression.

  (total motility must be specified if it includes PR + NP or just PR. The lower reference limit for a normal PR+NP is 40%, while for PR alone it's 32%).
- Immotility (IM): no movement.

Sperm vitality: it is clinically important to know whether immotile spermatozoa are alive or dead and is a useful parameter to know how many spermatozoa have an intact membrane. This parameter is usually studied together with sperm motility. The lower reference limit for vitality is 58%.

Sperm count: A sufficient number of spermatozoa is required; preferably at least 400 or 200 per replicate. If no sperm is observed in a semen sample, azoospermia might be the reason.

Sperm morphology: The observation of spermatozoa recovered from the female endocervical mucus after coitus and from the surface of the pellucid zone has helped to establish a pattern of normal morphological (potentially fertilizing) spermatozoa (Fig. 4). However, the analysis of sperm morphology is still difficult to standardize and has to take into account different types of defects along the structure of the spermatozoa. To assess abnormal sperm morphology, defects in the following parts should be noticed: tail, neck, head and an excess of residual cytoplasm (ERC). The lower reference limit for normal forms in a semen sample is 4%.

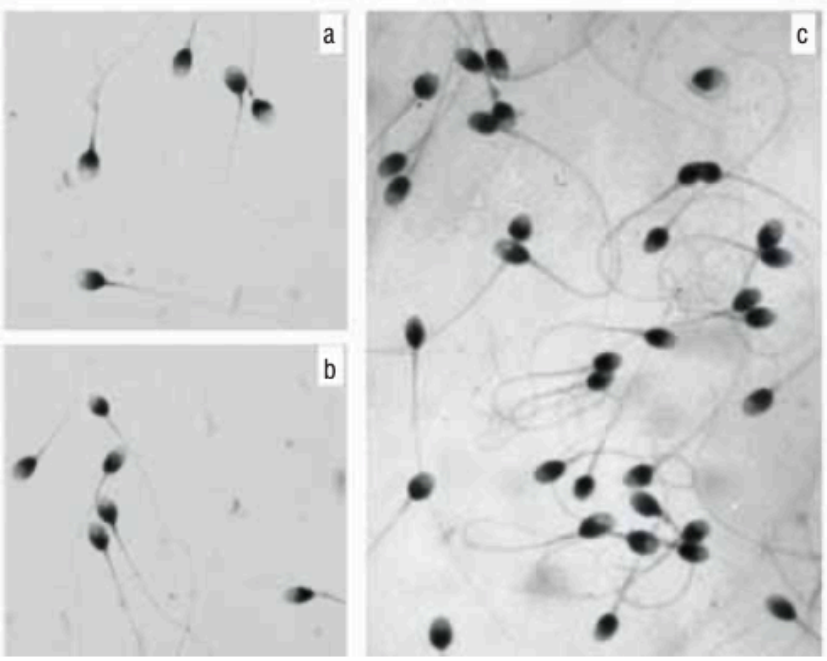

Figure 4. (a, b) Shorr-stained morphologically normal spermatozoa. (c) Papanicolau-stained morphologically normal spermatozoa. Image adapted from World Health Organization, 2010.

All these parameters of a semen analysis, which can also include pH, volume or viscosity need to be backed by a quality control in laboratories which have implemented a quality assurance (QA) program based on standardized methods and procedures, in order to avoid errors and variability of the results (WHO, 2010).

Since the quality of the sperm has been decreasing worldwide over the past few decades and an increase of the consumption of different processed food with high amounts of sugar as well as other unhealthy lifestyle habits, there has been an interest in finding out whether there exists a relationship between diet, lifestyle, and sperm quality. Another important question to solve is the repercussion of those factors (combined or separately) on different sperm parameters and how these might be affected from a cellular and molecular point of view while taking also into account the intra-individual variation that may interfere.

Until a few years ago, the most widely available studies were mostly observational, followed by experimental ones about the effect of different components of the diet on different semen parameters. Nowadays, a greater scientific approach is necessary to understand at a cellular, molecular and epigenetic level, how semen parameters and also the resulting offspring can be affected or altered as a result of consuming one type of dietary component or another.

Small and Transfer Ribonuclear Acid in sperm maturation

tRNA is considered a non-coding RNA molecule (ncRNA) that has an important function in synthesizing proteins. It transfers amino acid molecules to ribosomes and organizes them along the mRNA molecule. On the other hand, sRNA is a small molecule of RNA which may not be automatically a ncRNA, thus being coding or non-coding, and has been related to the ability to link to protein targets and alter the function of the linked protein. Also, sRNA is capable to interfere with targets of mRNA and modulate the expression of genes (Lamichhane et al., 2013).

Animal studies have been made in order to investigate how the offspring metabolism could be modulated when a specific diet pattern is administrated *in vitro*. Two different mice groups were established, one serving as the control group (19% of protein) while the other was administrated with a low-protein diet (10% of protein). The offspring was analyzed and showed a hepatic up-regulation of the gene which encodes for the enzyme squalene epoxidase, an important enzyme in the cholesterol biosynthesis. In the low-protein diet group, cauda sperm was isolated. During maturation of the sperm, significant cleavage of tRNA was observed in the epididymis. Since it has been found that sRNAs can be originated in multiple locations of the reproductive tract, the observation of the effects of a low-protein diet on sRNA was assessed in the testis and the epididymis. Changes in *5'* glycine tRFs (tRNA fragments) – tRF-Gly-GCC –, which may be generated in the epididymis and are transported to sperm by vesicles known as epididymosomes, and in let-7, a microRNA precursor, were observed in response to this low-protein diet. Moreover, by injecting sRNA

populations purified from control and low-protein sperm into control embryos, the discovery that low-protein RNAs could inhibit tRF-Gly-GCC targets (such as the endogenous retroelement MERVL) was made, thus meaning that paternal diet is able to affect gene regulation by sRNA in sperm. On the other hand, when the sperm of a low-protein diet mice was introduced into a female egg to fertilize it, ribosomal protein genes were seen to be down-regulated in low-protein embryos inducing a retarded development of these embryos compared to mice embryos of the control group (Sharma et al., 2016). Therefore, it can be considered that an adequate protein intake is important for the correct biogenesis of sRNAs in the masculine reproductive system.

Due to the fact that this molecular evidence demonstrated the importance of protein intake, it is necessary to know the different dietary meat options available on the market. Poultry meat, which is considered white meat because of its pale color before and after cooking seems to have interesting beneficial properties. Epidemiological studies focused on the impact of the ingestion of poultry meat and demonstrated that a higher intake of this meat is considered to be associated with a lower risk of suffering from azoospermia and with a higher fertility rate. However, other studies have shown inconsistent results and it has to be taken into account that such effects might be triggered by the way the animals are kept. For example, not all poultry is kept in the same way, given the same animal feed or treated with the same antibiotics on different farms. Such differences in breeding conditions might explain the observed variations and, thus, are a remaining factor that could lead to confusion when it comes to interpret the results obtained in the experiments. Therefore, it remains unclear whether the different results are really comparable or not (Salas-Huetos, et al., 2019).

A different option is red meat, a term usually referring to meat of mammals. The correlation between red meat intake and its effects on sperm quality parameters of adults has been investigated. It has been found that processed red meat intake has an inverse relationship with total sperm count in adults. The term “processed meat” refers to meat that has been manipulated in order to either preserve it or to enhance its flavors. Some examples of such processed meat are sausages, bacon and ham.
However, in countries like the United States and others, processed meat products usually come from animals such as cattle and this kind of livestock typically receives a hormonal cocktail of anabolic sex steroids. The mixture frequently contains progesterone, testosterone, estrogen, and sometimes also synthetic hormones such as zeranol or melengestrol acetate, all in order to increase the volume of the animal before slaughtering it. Although a so-called wash-out period has to be respected before slaughtering, the possibility of ingesting residual amounts of these hormones remains, if this meat is consumed. In this context, the results

regarding the intake of processed red meat with respect to sperm quality is somewhat diverse according to the variety of studies carried out. However, certain observational studies have found an increased risk of asthenozoospermia in men with a high intake of processed meat compared to men with a low intake (Nassan et al., 2018). Furthermore, also an inverse relationship with sperm morphology has been demonstrated by the consumption of organ meat, since in this kind of meat a bigger amount of copper is found and has been related to decrease sperm motility and morphology, thus related to oxidative stress and its consequent damage (Afeiche et al., 2014) – concept explained in page 23 –.

There are additional studies that focused on mothers with an elevated ingestion of beef consumption during pregnancy who gave to birth to males that 30 years later presented a low sperm concentration compared to those mothers that claimed no beef intake (vegetarian) during their pregnancy. Counting mostly with epidemiological studies and some of them with rather contrary conclusions to those mentioned above, it is difficult to establish a clear relationship between the intake of processed red meat and negative effects on sperm quality parameters, thus, corroboration from new and varied experimental studies is needed here (Afeiche et al., 2014).

In addition to meat, other dietary components such as seafood, i.e. fish or shellfish, are considered sources rich in proteins. However, in addition to proteins, these foods also supply ω-3 fatty acids with specific nutritional properties as they provide antioxidant and anti-inflammatory effects and compensate the proinflammatory effect caused by ω-6 fatty acids. Since humans are able to synthesize ω-6 but not ω-3 fatty acids, these fatty acids are considered essential and it is indispensable to include them as part of the diet. It has been observed that consumption of seafood has a beneficial impact on the count of spermatozoa and also their morphology. In addition, a change in the diet replacing red meat with a higher consumption of fish, seems to have beneficial impacts in relation to the quality of sperm (Afeiche et al., 2014). However, if the fish or shellfish are contaminated with methyl mercury, these potential beneficial effects might be compensated by the toxic effect of this compound. Negative effects of methyl mercury on male reproduction have been seen in both *in vivo* and *in vitro* studies and include a wide array of effects, such as dysfunction in spermatogenesis, underweight testes, sperm with abnormal tail morphology, and decreased sperm count and motility. Furthermore, carrying out studies using mercury measurements in the hair (considered one of the best biomarkers for mercury exposure), a positive correlation between mercury exposure and altered semen parameters - total sperm count, sperm concentration and total motility in men – could be corroborated. Still, the dietary benefits of seafood for

spermatogenesis may outweigh the adverse effects of ingested mercury and depend on the seafood source and its contamination level (Nassan et al., 2018).

The effect caused by a specific type of diet of fertile males on the metabolism of their offspring has also been studied, and it has been found that it can lead to various metabolic disorders and alterations in gene expression, although the exact molecular mechanisms are largely unclear. In detail, the effect of a high fat diet (HFD) has been studied in male mice and it could be observed that different sperm transfer ribonuclear acids (tsRNA), are capable of causing changes in expression profiles as well as RNA modifications. Therefore, it seems that these tsRNAs act as a paternal epigenetic factor that transmits a genetic inheritance to the offspring of suffering metabolic disorders and thus being a direct result of the parental intake of a high-fat diet (Chen et al., 2016). Also, dietary sugar and obesity has been seen to affect and modulate specific subtypes of tsRNA – which include nuclear and mitochondrial tRNAs – (Nätt et al., 2019). However, since mice and humans share more than 95% of genes, the effects caused in the mouse may be extrapolatable to humans, thus corroborating epidemiological studies in males indicating that a high fat intake decreases the quality of sperm.

Since a HFD has been related to affect tRNAs, it's also important to discuss the fact that a high-fat diet leads to increased cholesterol levels and this has been associated to alter semen parameters in a negative way. Changes in the lipid content could be detected in the testis and in epididymal cells as well, thus, increasing sperm with abnormal morphology, altered basic sperm functions – such as sperm capacitation or sperm motility (among others). It has been seen that these changes in sperm quality parameters are based on a dysregulation in the organization of membrane lipids and proteins, which seems to compromise the functionality of the sperm when it comes to being able to cross the pellucid zone of the ovule. It has been seen in rabbits that cholesterol may be related to the rigidity of the membranes and the loss of its sperm capacitation, however a daily supplementation of virgin olive oil to the fat diet improved the sperm quality and decreased hypercholesterolemia of these rabbits to normal levels (Lancellotti et al., 2013). However, these findings in animals still remain to be confirmed in clinical studies in humans.
Also, it has been shown that males doing physical exercises with a proper intensity and frequency on a regular basis have better semen quality parameters (progressive and total motility, higher viability and a lower percentage of dying sperm cells) than males with a sedentary lifestyle. A physically active life style also lowers the risk to develop obesity and, consequently, seems to protect the spermatozoa. All this shows that the so-called healthy

lifestyle has to be considered as another conditioning factor being able to maintain different seminal parameters at physiological levels (Lalinde-Acevedo et al., 2017).

Since dietary sugar has been shown to affect different tsRNA, the impact of the intake of sugar-sweetened beverages (SSBs) on sperm quality has been studied in young healthy males. As a result, SSBs have been shown to cause lower sperm total and progressive motility, but no other semen parameters where altered, thus being consistent with experiments done in rodents. The effect of SSBs on human metabolism has been associated with increased insulin resistance in both adolescents and adults. This insulin resistance and even in type II diabetic people, has been observed to increase oxidative stress and, thereby, influencing in a negative form on sperm motility (Chiu et al., 2014). However, other studies claim that there is no relation between sugar and semen quality, thus, more clinical studies are required to establish, if a statistically significant correlation exists.

Finally, the typical Western Diet pattern, which is characterized by the intake of larger quantities of red and processed meat, sugar, a high amount of fat and sugar-sweetened beverages, has been associated with a higher risk of suffering asthenozoospermia and decreased sperm quality parameters. Therefore, males who follow this type of diet are more prone to deteriorate their sperm on a molecular and cellular basis and to suffer male infertility (Eslamian et al., 2016).

Sperm DNA Fragmentation (SDF)

This term refers to the presence of abnormal genetic material in the sperm, which can consequently lead to infertility. Sperm nuclear condensation, which takes place during spermiogenesis, is a complex sequence of molecular events, such as the transition of DNA-binding proteins, changes in DNA transcription and the loss of the nuclei form. In deficient sperm, activity of the endogenous nuclease has been suggested to produce and join nicks on DNA strands during spermiogenesis, while these nicks are not identified in normal mature sperm. Transition proteins (TPs) are presumed to have the capacity of repairing these DNA nicks, thus leading to obviate persistent DNA damage to mature sperm. Furthermore, any adjustments in the epigenetic mechanisms of the spermatozoa molecular contribution to the fetus, for example, histone alterations, particular histone retention, transcription factors, DNA methylation, among others, can inhibit an accurate delivery of the paternal genome to the oocyte and consequently influence negatively the sperm purpose. Modifications that occur in any stage of the condensation process of chromatin might have severe consequences on sperm function. However, the presence of sperm DNA damage is typically related to the next significant mechanisms: 1. abortive apoptosis during meiosis I producing spermatozoa that,

although they are defective, are able to evade the apoptotic pathway; 2. deficient chromatin condensation throughout spermiogenesis; 3. Testicular oxidative stress as a result of an excessive presence of reactive oxygen species (ROS); 4. fragmentation induced by side effects of various pathologic iatrogenicities and environmental circumstances which include: antineoplastic drugs, varicocele, cancer, high fever or air pollution, among others, that all may have an important regulatory impact on sperm vitality and sperm motility (Evgeni et al., 2014).

Some dietary components, such as nuts, fruits, vegetables, soy-derived products, coffee and some antioxidants like Zinc, have shown to have an impact on SDF. Zinc (Zn) is an important trace mineral because it is necessary for the body's immune system to function properly and also participates in the division and growth of cells. In sperm cells, Zn is a very important mineral to stabilize the membrane since it inhibits the binding of oxidative enzymes like NADP oxidase to the membrane, thus increasing sperm concentration and sperm motility. Zinc is also necessary for sperm DNA to condense and de-condense properly. Furthermore, some studies in humans have suggested that Zn is responsible for regulating the chromatin stability of ejaculated sperm and that it would also regulate the formation of disulfide bridges. Indeed, a low intake of Zn has been linked to cases of male infertility (Salas-Huetos et al., 2019) and one of the reasons could be that the stability of the sperm chromatin would appear compromised since a lack of Zn hiders to regulate this and could lead to non-viable spermatozoa.

The impact of nuts intake on sperm quality has been studied experimentally by Randomized Controlled Trials (RCTs). Nuts are well known for being a food source rich in fiber, minerals, different types of antioxidants and fatty acids. Indeed, most nuts contain approximately 50% of fatty acids, most of which are monounsaturated fatty acids (MUFAs) while walnuts contain mostly polyunsaturated fatty acids (PUFAs). It has been observed that an intake of 60 g of a mixture of nuts in the experimental group that followed a Western Diet pattern for 14 weeks has been shown to improve total sperm count, vitality, motility, and morphology compared to a control group. In the same way, in a previous study by consuming 75 g of walnuts for 12 weeks in the experimental group *vs.* a control group, improvements were seen in the same seminal parameters, thus claiming an improvement in sperm quality. Other studies also explored the effect of administering a mixture of nuts (almonds, hazelnuts and walnuts) in a Western-style diet for 14 weeks as well, and showed that this administration improved in a significant way various sperm parameters such as vitality, motility, morphology and the total spermatozoa count (Salas-Huetos et al., 2018).

Also, a regular consumption of vegetables and fruits provides an important number of antioxidants, which are essential for the proper functioning of the body and the sperm, because these antioxidants act as sperm ROS regulators by increasing the motility of the spermatozoa and reducing SDF. Also, by the intake of these foods, folate, which is included in the vitamin B group, is ingested. Folate seems to have a series of positive effects on sperm quality, such as lowering the risk of sperm aneuploidy. Therefore, it is thought that folate might be associated with correct spermatogenesis and the prevention of SDF (Young et al., 2008).

On the other hand, isoflavones, which are phytoestrogens pertaining to the group of plant estrogens, can be found in plants such as soybeans and soy-derived products. In experimental studies with rats, these isoflavones have been shown to cause shrinkage of rat testes and to cause negative effects on sperm capacitation as well as acrosomal reaction, although in humans conclusive studies are still missing. In supplementation studies with isoflavones in males for 2 months, not many statistically significant changes could be detected between the time before and after the supplementation. However, a certain increase of sperm concentration and motility as well as a reduced damage to sperm DNA or SDF was observed. In other studies, including men with infertility of unknown cause, isoflavones in urine were analyzed and elevated levels were associated with a lower concentration of sperm, lower sperm count and motility, as well as a greater probability of suffering infertility (Nassan et al., 2018). Due to the inconsistent results of these studies, it is important to carry out a greater number of clinical experiments to reveal the actual relationship between this type of product and its effects on semen quality, if there exists any.

In this line, the findings of epidemiological studies focused on coffee intake and, in particular, the effect of caffeine, are as well incongruent and inconsistent. In some studies, it has been observed that caffeine could negatively affect sperm quality through sperm DNA damage (Ricci et al., 2017). Nevertheless, in more recent studies that have been carried out experimentally in scopolamine-induced rats, caffeine intake has been related to a positive impact on sperm quality. In this context, scopolamine is a compound that negatively alters seminal parameters and increases ROS. It has been demonstrated that caffeine helped to regulate the activity of steroidogenic enzymes in scopolamine administered rats, increased thyrotropin hormone (TRH) levels in testicular tissue, decreased abnormal sperm levels and increased sperm motility, reduced ROS and prevented from oxidative stress in epididymal and testicular tissues (Akomolafe et al., 2019).

In any case, not only separated dietary components but one concrete type of diet pattern has been linked to a decreased risk of SDF, which is the health-conscious dietary pattern. This pattern includes mostly the consumption of vegetables, fruits, fish, whole grains and legumes and it could be demonstrated that this diet leads to a lower sperm DNA fragmentation compared to other dietary patterns (Vujkovic et al., 2009).

Diet and Male Reproductive Epigenetics

Studies in biological and medical research focused on epigenetic inheritance are currently in trend. Epigenetics are considered the research of the mechanisms that control the expression of genes with no modifications in the sequence of DNA and it establishes the connection among the gene and environmental influences that define a phenotype. Sperm has a series of unique epigenetic marks, consisting of: their DNA methylation profile; proteins associated with DNA; the ratio of protamines, which are small, arginine-rich nuclear proteins responsible for replacing histones at the end of the haploid phase of spermatogenesis and are considered essential for condensation of the sperm head and DNA stabilization; nucleosome distribution; post-translational modifications of the histones; the amount of RNA stored as well as other proteins that are not protamines.

In order to study the effects of the diet on epigenetic marks, it is necessary to take into account a series of clarifications. The magnitude of the change in the epigenetic mark will be different depending on the type of food or ingredient used. In addition, if a dietary pattern is used instead of a single nutrient, it may produce different results because in the first case it will probably act more than only one diet component and there may be a series of cross interactions that are undesired or that cannot be explained in a straight way. On the other hand, the results that can be extracted from an epidemiological study carried out over 3 months will possibly not be similar to a study that has lasted twice as long. Physical exercise must also be monitored in this type of study, as it is also able to influence epigenetic marks, thus, modulating the results that a diet alone could produce in an individual. The microbiota is likewise associated with epigenetics, since its function is related to the correct absorption of certain minerals, such as zinc or selenium, which are important enzymatic cofactors in spermatogenesis (Schagdarsurengin & Steger, 2016).

However, it is rather unlikely that diet actually is able to affect the sperm epigenome, since sperm cells have condensed DNA chromatin. As a consequence, it is not transcribed and is differentiated without any subsequent cell division, a perquisite for epigenetic modifications. Therefore, the target of epigenetic modification is the germ cell found in the testicles and not the mature spermatozoa. Also, dietary factors are not able to directly change epigenetic marks, but they have been seen to act on enzymes that are capable of adding or removing

these epigenetic marks to DNA and histones. Epigenetic regulation of transcription can occur either by modifying methylations or acetylation of DNA and / or histones as well as by epigenetic regulation of the translation via ncRNAs. For methylation and acetylation processes, methyl or acetyl groups are necessary and can be incorporated from different components of the diet, such as folate or vitamin B12, among others. These components are donors of methyl groups that will be placed into the methionine cycle and the folate cycle, used by the S-adenosylmethionine (SAM) molecule. Food provides carbohydrates or fatty acids, that can be used to obtain acetyl groups (for example, in the process of β-oxidation of fatty acids) generated in the mitochondria and transferred by the acetyl-CoA (ACAT) molecule. Both acetyl and methyl groups can be used by a variety of enzymes such as histone acetyltransferases or DNA methyltransferases that modify histones or methylate or demethylate DNA thereby regulating the epigenetics of germinal cells that finally differentiate to fully developed sperm cells (Fig. 5) (Rice & Allis, 2001).

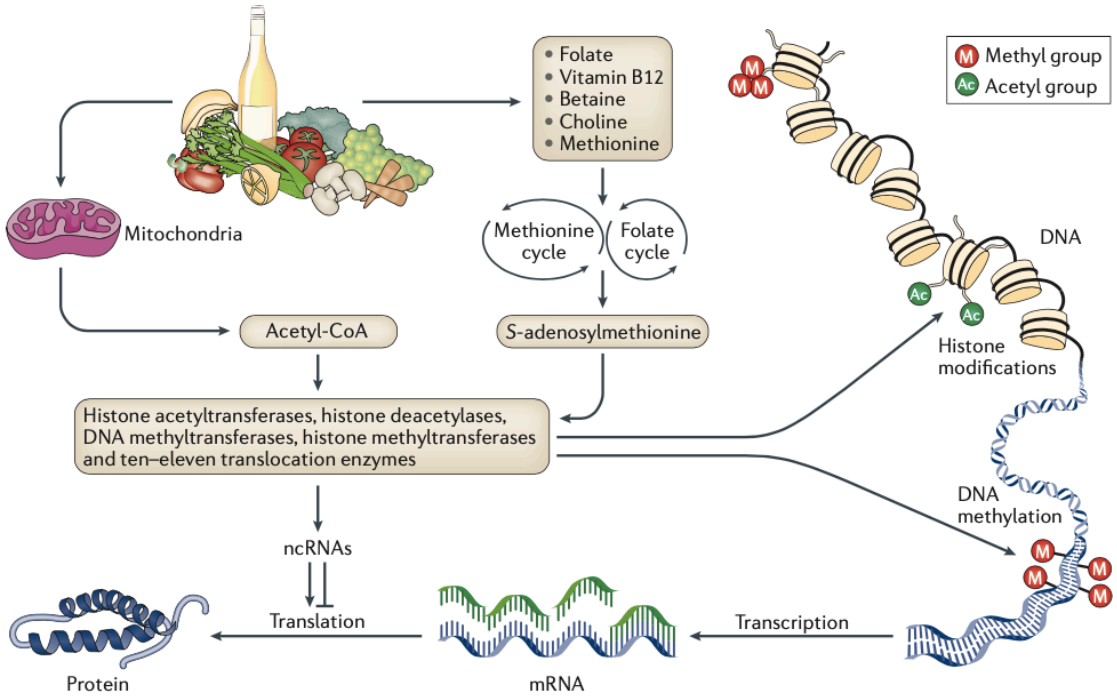

Figure 5. The role of different diet components in epigenetic processes. Image from Schagdarsurengin & Steger, 2016.

As mentioned above, it has been observed that components like folate, vitamin B12, fatty acids, zinc or selenium play a role in the epigenetics affecting key enzymes to add/remove epigenetic marks to DNA of the germ cells that will develop into mature sperm during spermatogenesis. Also, all these components have shown to play a key role in oxidative stress conditions.

Research studies that have been carried out so far indicate that different factors, including dietary compounds, can modulate the epigenetics of germ cells and thus the sperm, which are eventually transferred to the oocyte during fertilization and, therefore, can affect the embryonic development as well as the health of the offspring during its entire life. However, up to date it has not been established in detail which nutritional factors trigger which molecular mechanisms involved in epigenetic marks and if these factors may prevent or modify specific epigenetic regulation related to male's sperm quality (Schagdarsurengin & Steger, 2016).

Oxidative Stress

Oxidative stress has been found to be one of the causes that can cause male infertility. To study how oxidative stress may affect human sperm, different studies have been carried out. Oxidative stress occurs when there is an imbalance in our cells due to an increase in free radicals and/or a decrease in antioxidants. Radicals are chemical species with a high potential of oxidizing molecules. On the other hand, an antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules by being oxidized instead. Over time, a permanent mismatch in the cellular balance between free radicals and antioxidants can damage the tissues. Such imbalance occurs when there is an excessive amount of reactive oxygen species or ROS in comparison to the amount of antioxidants, thus leading to a harmful biochemical situation for the cell. ROS include oxygen free radicals like the superoxide anion radical (O_2^-) which is especially important as the product of the one-electron reduction of dioxygen, the extremely aggressive hydroxyl radical anion ($OH\cdot$) derived from subsequent chemical reactions, the singlet oxygen ($^1O_2$) and non-oxidizing agents; in addition, nitric oxide ($NO\cdot$) and derived peroxynitrite radical ($ONOO^-$) can be included in this category. The mitochondria's respiratory chain is the principal source of ROS, primarily O_2^- and consequently hydrogen peroxide (H_2O_2) and there are two major respiratory chain regions where ROS are produced, one is the complex I and the other one is the complex III (Lenaz, 1998). The origin of ROS in sperm has been further determined in detail and an important source of ROS generation is a disruption of the flow of mitochondrial electron transport in human sperm. The induction of ROS on the matrix side of the inner mitochondrial membrane in complex I causes peroxidative damage and therefore, a loss of sperm movement. These findings propose that sperm mitochondria contribute to the oxidative stress of defective human sperm (Lanzafame et al., 2019).

However, ROS are tangled in the control of normal sperm function. Since a normal amount of different types of ROS maintained during spermatogenesis is important for sperm capacitation, the acrosome reaction and for spermatozoa to mature, a later increase in seminal ROS is possible and has been related to infertile men. Two different courses

contribute to the production of ROS and the resultant infertility: on the one hand, the reduced NADPH (Nicotinamide Adenine Dinucleotide Phosphate Hydrogen) oxidase system that produces superoxide that is converted to peroxide by the action of SOD (Superoxide dismutase) which occurs on the plasma membrane of sperm and, on the other hand, the reduction of NAD (Nicotinamide Adenine Dinucleotide) dependent oxidoreductase (diphorase) at the mitochondria (Fig. 6) (Lanzafame et al., 2019).

These ROS have been shown to have an impact on fertility mainly because they produce lipid peroxidation and DNA damage. Lipid peroxidation consists in the oxidative damage of lipids present in the plasma membrane, in organelles or even in lipoproteins. If an oxidative stress situation occurs, humans are oxidizing lipids that are present both in membranes and in lipoproteins. This is problematic since it can end up destroying the entire cell membrane and, thus, leading to the subsequent destruction of the entire cell (Hosen et al., 2015). Besides, a hyper-production of ROS has been found to worsen various sperm quality parameters such as sperm motility, capacitation, the acrosome reaction, the ability to fertilize the egg and the DNA integrity by causing nucleotide modifications in the nucleus of the sperm, strand break of the DNA and chromatin cross-linking (Lanzafame et al., 2009).

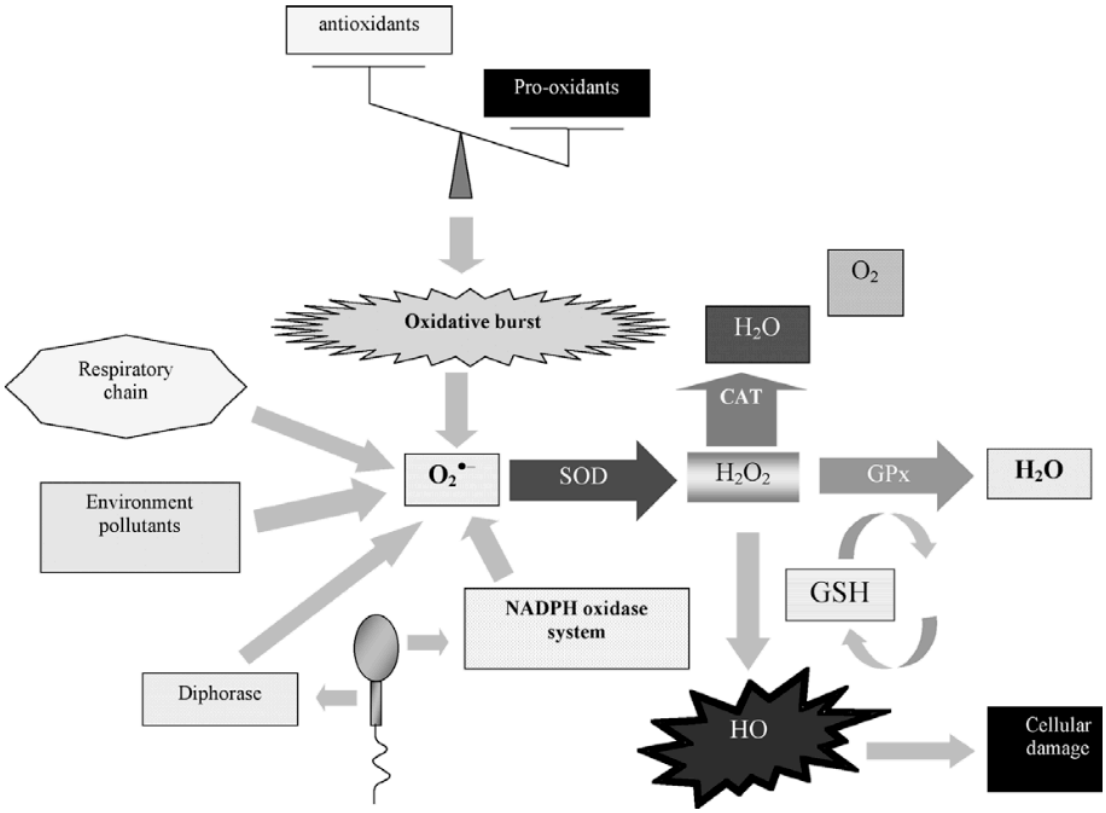

Figure 6. Representative diagram of reactive oxygen species effects leading to cellular damage. GSH= reduced glutathione; SOD= superoxide dismutase; CAT= catalase; GPx= glutathione peroxidase. NADPH = nicotinamide adenine dinucleotide phosphate hydrogen. Image from Lanzafame et al., 2009.

Normally, an increase in ROS is usually controlled by the antioxidant system of the cell, as well as by the presence of substances that can be peroxidized, in this case the polyunsaturated fatty acids (PUFAs), among which one of the fatty acids that appears in higher concentrations is the docosahexaenoic acid (DHA). Low concentrations of DHA, total PUFA, and ω-3 fatty acids, may be the reason of a hyper-production of ROS. Nevertheless, since PUFA encompasses ω-3 fatty acids and ω-6 fatty acids, it's important to remark that ω-6 fatty acids have pro-inflammatory properties, whereas ω-3 fatty acids have anti-inflammatory properties, which makes important the maintenance of an adequate balance of the ω-6/ω-3 ratio, preferably 1:1. (Lanzafame et al., 2009).

Besides, studies focused on the PUFAs ω-3 which have shown that these do help to decrease the levels of ω-6 fatty acids with pro-inflammatory properties – meaning they possess anti-inflammatory and antioxidant properties – thereby reducing the risk of different cardiovascular diseases. In the group of ω-3 fatty acids, three different types can be found: α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and DHA, which humans are unable to synthesize making them essential food components and their external supply an indispensable dietary requirement. These fatty acids have shown to have a positive effect on sperm quality parameters like an increase in the total sperm count and sperm motility, and some studies have also suggested that during spermatogenesis they incorporate into the spermatozoa cell membrane in order to maintain the lipid bilayer. Also, it has been seen that an adequate balance of ω-6/ω-3 ratio in the sperm cell membrane has been related to the maintenance of proper cell function avoiding the negative effects of oxidative stress by their antioxidant activity (Safarinejad & Safarinejad, 2012).

In general, it can be considered that ROS are an important factor in male fertility and can be generated by a variety of factors where one of the more important ones is a low intake of certain dietary components (mainly antioxidants). Therefore, it is crucial to stress the importance of an adequate intake of these antioxidants (Table 2) in order to be available as cofactors for some enzymatic antioxidant molecules such as SOD, CAT (Catalase) or GPx (Glutathione Peroxidase) and to protect cells from the damage than can be produced by an excess of the corresponding free oxygen radicals (Wright et al., 2014).

Vitamin C	Vitamin E	Zinc	Selenium
Papaya	Spinach	Spinach	Halibut fish
Bell peppers	Swiss chard	Shiitake mushrooms	Tuna
Strawberries	Sunflower seeds	Cremini mushrooms	Cod fish
Pineapple	Almonds	Organic lamb	Shrimps
Kiwi	Asparagus	Organic beef	Cremini mushrooms
Oranges	Bell peppers	Scallops	Mustard seeds
Broccoli	Cayenne pepper	Sesame seeds	Sardines
Cantaloupe	Papaya	Pumpkin seeds	Salmon
Kale	Kale	Oats	Turkey
Cauliflower			Barley

Table 2. Food sources of different antioxidants. Adapted from Wright et al., 2014.

Not only a balanced intake of fatty acids or the intake of vitamins (E, C) and minerals like zinc or selenium are important by acting as antioxidants, since different dietary components have shown to play a role in oxidative stress. Since selenium (Se) acts like an antioxidant, its effect has been studied in humans and revealed that a high intake of this mineral might be associated to alterations regarding male fertility related to a lower sperm motility. Due to the fact that sperm is particularly sensitive to oxidative stress, some researches have focused their studies in finding out how antioxidants like Se prevent the appearance of ROS. It seems that Se increases the activity of glutathione peroxidase-1 (GPx1) and eliminates molecules of hydrogen peroxide and reduces the ROS production in the spermatozoa (Hawkes & Turek, 2001).

Also, there have been made studies focused on how other supplements like carnitines mixed with antioxidants may have an impact. L-acetyl carnitine (LAC) and L-carnitine (LC) function as a transporter of long-chained fatty acids into the mitochondria, thus, providing energy for the spermatozoa. Therefore, it has been considered that carnitines may positively impact on sperm motility. Evidence has been found that dietary supplementation of carnitines combined with antioxidants might also regulate other sperm quality parameters, thus, influencing male fertility. However, more clinical evidence is needed to determine the correct doses of supplements and antioxidants able to induce a positive outcome without triggering adverse effects, such as an increased oxidative stress due to overdosing (Salas-Huetos et al., 2019).

Another research group focused on studying the GGNBP1 protein (Gametogenetin binding protein 1) with the aim of observing the functional effect of this protein, which is located specifically in the mitochondria of spermatocytes in the testes. In humans its gene is located

on chromosome 17 and in mice on chromosome 6. A study with knock-out (KO) mice used the novel CRISPR-Cas9 technique to compare mice of the control group (mice Ggnbp1$^{+/+}$) and the mice of the experimental one (mice Ggnbp1$^{-/-}$). The experiments revealed a defective spermatogenesis of the KO mice, showing changes in sperm morphology (abnormal head or tail) and a general reduction in sperm quality parameters. In order to test the stress that could be induced to the mitochondria (which are very numerous during the spermatogenesis process) of the KO mice, the drug BPA (Bisphenol A) was used. The results demonstrated an increase in the sensitivity of these mitochondria to external factors and leads to the conclusion that GGNBP1 function is important to ensure a correct spermiogenesis, if the cells are exposed to different types of environmental stress (Han et al., 2020). These external stress factors could be substances that might be found in different types of food or in drinking water, thus affecting and modulating spermiogenesis, eventually influencing sperm production and, therefore, compromising the male reproduction process. Nevertheless, massive sequencing studies would be necessary to rule out so called off-target events, which refer to nonspecific and unintended genetic modifications by the use of engineered nuclease technologies such as the CRISPR-Cas9 technique. A broader sperm sampling and thorough analysis of oxygen consumption, ATP synthesis and mitochondrial membrane potentials would also help to establish better its complete function in the mitochondria.

Ultimately, oxidative stress has been seen influenced positively by the Mediterranean Diet pattern. This type of diet is based on a high consumption of different types of food such as olive oil, nuts, vegetables, fruits, legumes, cereals, and a lower ingestion of eggs, fish, seafood, poultry, low-fat dairy products, spices and condiments, and also beverages like tea or coffee. The consumed food products provide different components such as antioxidants, fiber, polyphenols, ω-3 fatty acids or MUFA with an important role in oxidative stress. The high consumption of olive oil, for example, which is rich in MUFAs, is able to decrease lipid peroxidation due to the fact that it only provides one unsaturation unlike PUFAs that increase the probability of lipid peroxidation. Also, olive oil contains polyphenols, which are antioxidant molecules that act by directly eliminating ROS and / or increasing the activity or expression of endogenous enzymatic antioxidant molecules (Gambino et al., 2018). Therefore, the Mediterranean Diet has been considered one of the healthiest diets that is beneficial to human health in general and also contributing to affect positively the semen quality, such as a higher sperm count, sperm motility and lower risk of asthenozoospermia (Salas-Huetos et al., 2019).

Conclusions

The principal molecular mechanisms by which dietary components influence the quality of human sperm are:

- Sperm sRNA and tRNA (modulated differently depending on the protein source, by sugar sweetened beverages and by fat, leading to changes in sperm count).
- Sperm DNA Fragmentation (modulated by a variety of dietary compounds, leading to changes in sperm vitality or motility).
- Sperm epigenome (modulated by zinc, vitamin B12 and other essential food components acting on the germ cells).
- Reactive oxygen species (modulated by vitamins and trace elements, leading to changes in several sperm quality parameters).

Among the types of diet patterns, the Mediterranean Diet has turned out to be the one that contributes the highest number of components with a positive effect on sperm quality, whereas the Western Diet contains more components negatively related to those parameters.

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