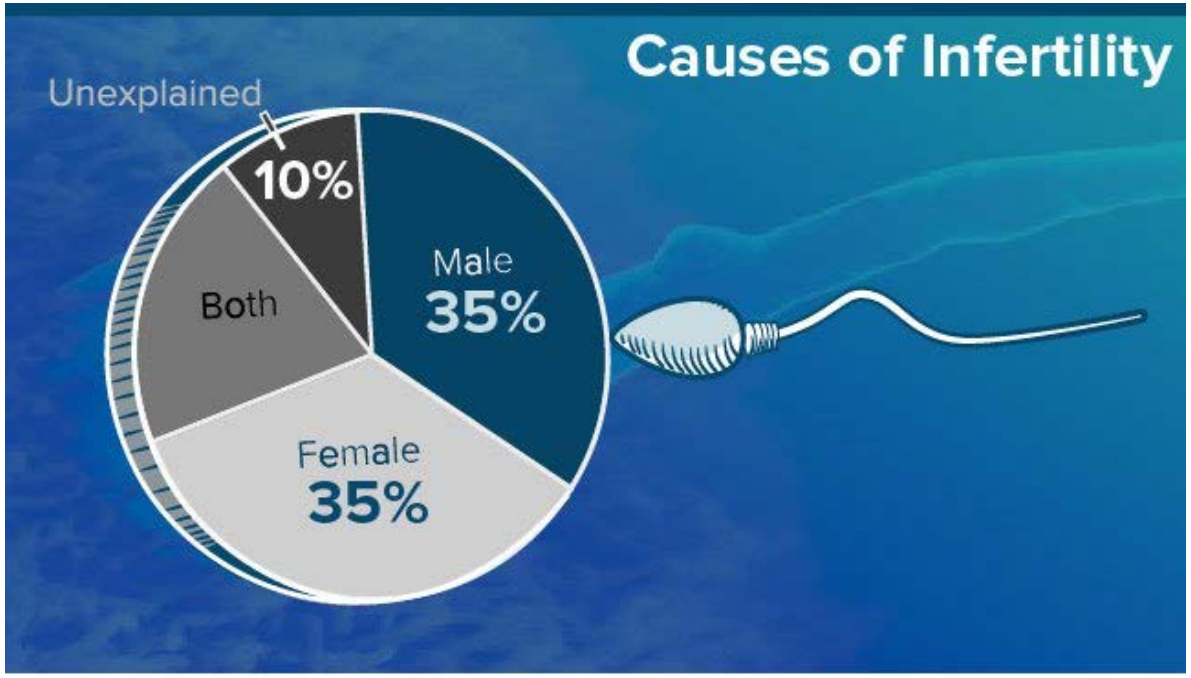
IN THE NAME OF GOD

OBESITY AND MALE INFERTILITY

Dr Ehsan Otroj M.D
Fellowship of Andrology at Tehran University

Male factor is 50 % of causes of infertility

- 1 in 5 couples suffer from infertility in IRAN
- about 5 million couples with infertility



Hum Reprod Update. 2017 Nov 1;23(6):646-659.

Temporal trends in sperm count: a systematic review and meta-regression analysis.

Levine H[1,2], Jørgensen N[3], Martino-Andrade A[2,4], Mendiola J[5], Weksler-Derri D[6], Mindlis I[7], Pinotti R[8], Swan SH[7].

- **The comprehensive study involved 42 935 men with samples spanning over40 years.**
- **They reported a significant decline of 50– 60% in sperm counts amongst men from North even greater concern over the reasons behind the apparent America, Europe, Australia and New Zealand .**
- **This latest finding has sparked line in the sperm count of Western men**

CAUSES OF INFERTILITY IN MALES

OBESITY

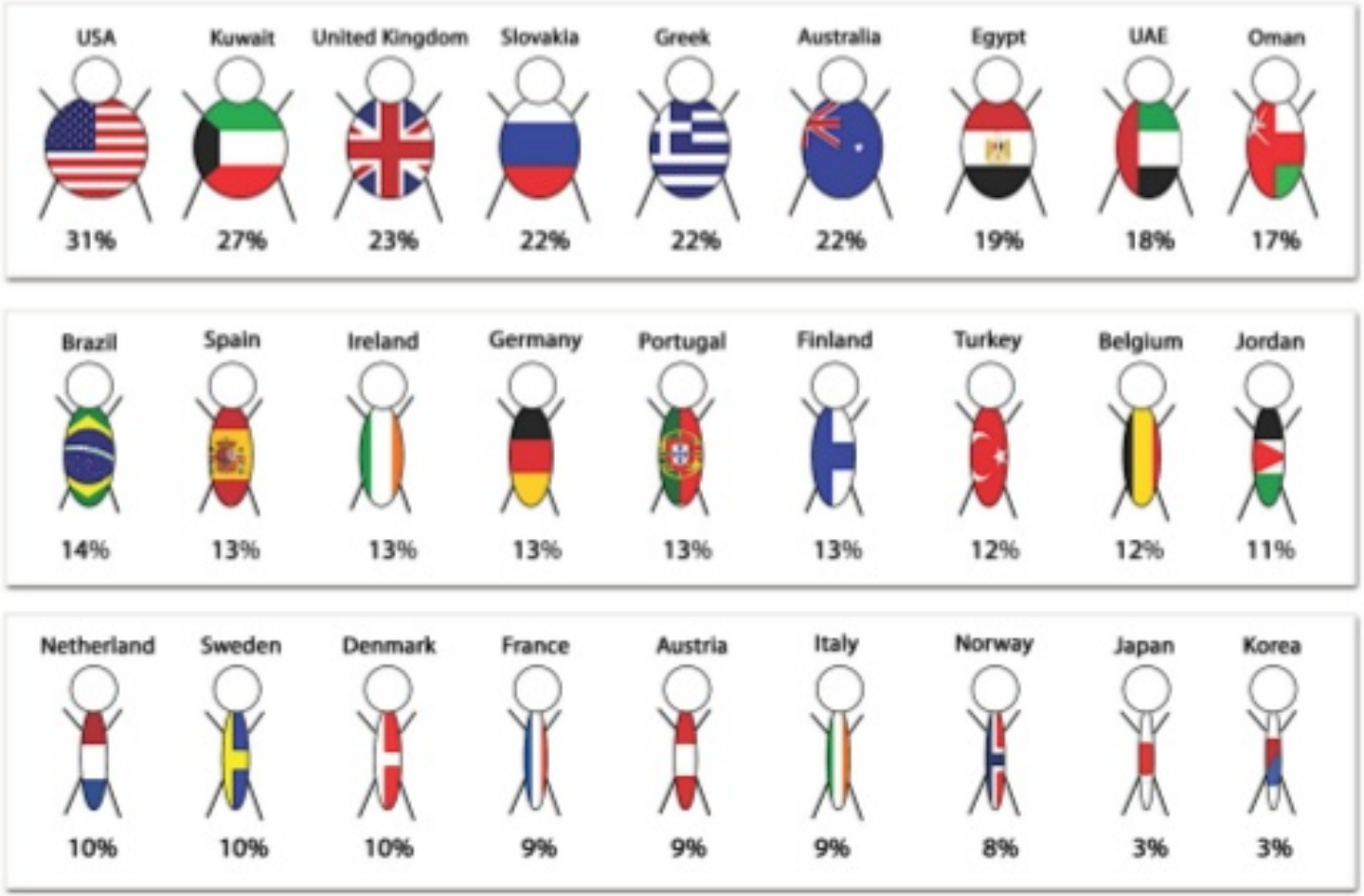
- Approximately 1.9 billion people are overweight (body mass index (BMI) ≥25 kg/m2) or affected by obesity (BMI ≥30 kg/ m2) in the world (World Health Organization 2014) and are at risk of developing type 2 diabetes, cardiovascular disease and related metabolic and inflammatory disturbances.
- obesity was associated with a more than 20% increased cases of subfertility and infertility

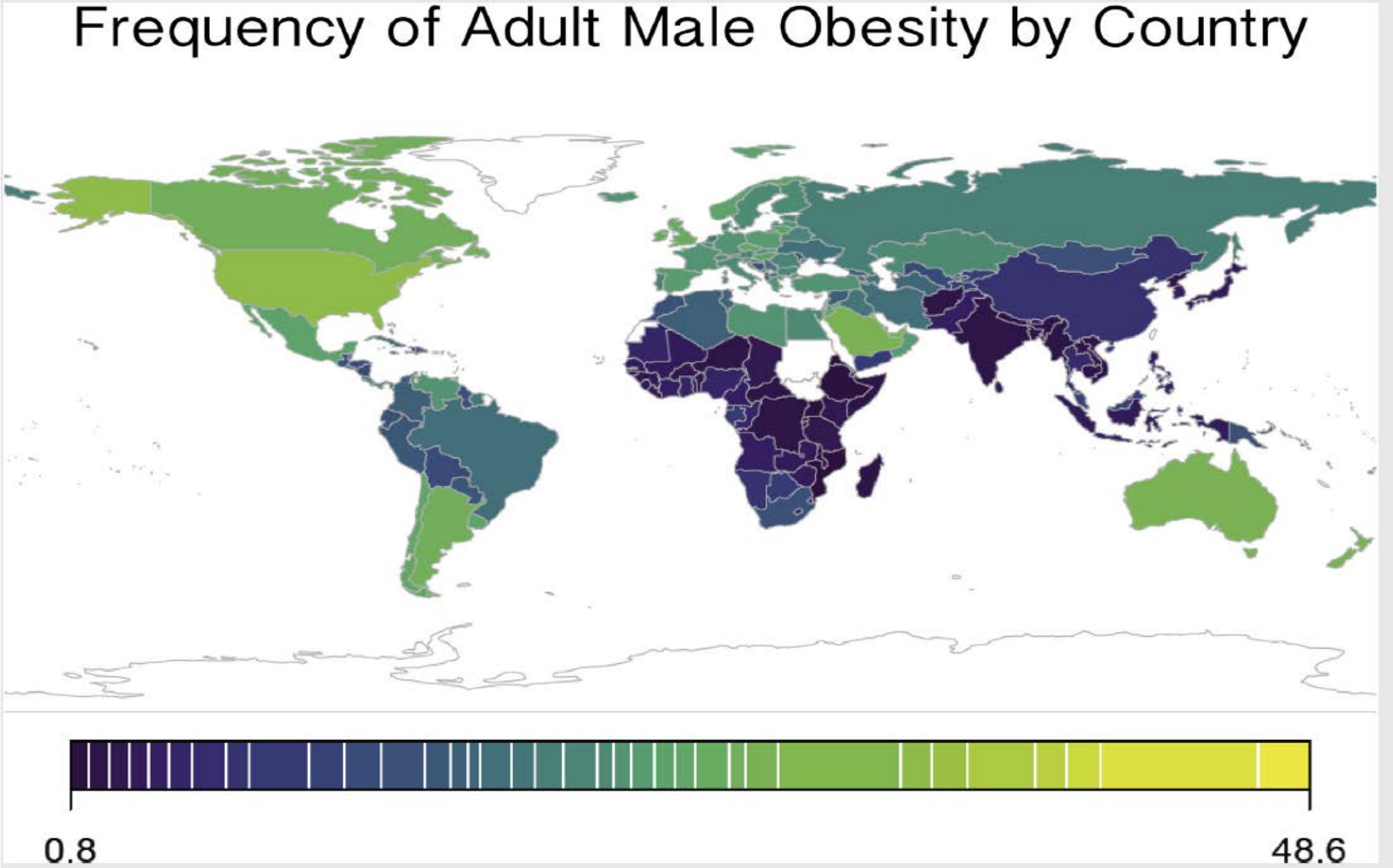
OBESITY

DEFINITION OF OBESITY

BMI (kg/ m2)	Class
25.0 -29.9	Overweight
30.0 – 34.9	Obesity Class I
35.0 – 39.9	Obesity Class II
40 or more	Obesity Class III or Extreme Obesity

Obesity in Men at Reproductive Age




Frequency of Adult Male Obesity by Country
0.8
48.6

OBESITY IN IRAN

تاریخ انتشار : دوشنبه ۱۵ خرداد ۱۳۹۶ ساعت ۲۳:۰۵
مدیر کل دفتر بهبود تغذیه جامعه وزارت بهداشت، درمان و آموزش پزشکی گفت: تغییر الگوی غذایی و کم تحرکی در جامعه، اضافه وزن و چاقی برای 60 درصد مردم را در پی داشته است.

به گزارش ایران خبر، زهرا عبداللهی روز دوشنبه در گفت وگو با ایرنا در مورد آخرین وضعیت اضافه وزن و چاقی در کشور اظهار کرد: وزارت بهداشت در مطالعات مختلفی به صورت مقطعی در مقاطع سه ساله و پنج ساله بررسی های کشوری انجام می دهد که در همه سطح کشور گروه های سنی مختلف نمونه آماری گرفته می شود.

وی افزود: این مطالعات معمولا با پرسشگری، مصاحبه، اندازه گیری قدو وزن و محاسبه توده بدنی/ BMI و حتی نمونه خون انجام می شود.

مدیر کل دفتر بهبود تغذیه جامعه در وزارت بهداشت، درمان و آموزش پزشکی ادامه داد: یک نمونه از این مطالعات کشوری مطالعه «عوامل خطر بیماری های غیرواگیر» است. این مطالعه در همه کشورها با استانداردهای یکسان انجام شده و اصطلاحا به مطالعه STEPs/ استپس معروف است.
«در این مطالعه شیوع اضافه وزن و چاقی، شیوع فشار خون بالا و کلسترول بالا بررسی می شود».

***60 درصدجمعیت گرفتار اضافه‌وزن و چاقی هستند

وی با اشاره به اینکه این مطالعه آخرین بار سال 95 انجام شده گفت: این مطالعه یکبار سال 91 و آخرین بار سال 95 انجام شده و معمولا بازه زمانی آن چهار یا پنج سال یکبار برای بررسی روند کلی چاقی در کشور است.

عبداللهی تاکید کرد: اکنون مقایسه نتیجه این دو مطالعه نشان می دهد؛ شیوع چاقی و اضافه وزن در کشور بیشتر شده است و به طور متوسط 60 درصد جمعیت 15 تا 64 ساله چاق هستند. همچنین در گروه های سنی مختلف 45 تا 55 سال و 55 تا 65 سال این رقم به 70 تا 75 درصد می رسد، ضمن اینکه شیوع چاقی و اضافه وزن در همه گروه های سنی خانم ها خیلی بیشتر است.

Jafari-Adli *et al. Journal of Diabetes & Metabolic Disorders*
DOI 10.1186/s40200-014-0121-2

Journal of Diabetes & Metabolic Disorders

REVIEW ARTICLE Open Access

Prevalence of obesity and overweight in adults and children in Iran; a systematic review

Shahrzad Jafari-Adli[1], Zahra Jouyandeh[1], Mostafa Qorbani[2,3], Ahmadreza Soroush[1], Bagher Larijani[4] and Shirin Hasani-Ranjbar[1,4*]

The range of overweight and obesity prevalence in national studies in adult, was 27.0-38.5 (95% CI: 26.8-27.1, 37.2-39.8), and 12.6-25.9 (95% CI: 12.2-13.0, 24.9-26.8), separately.

In under-18 the range of overweight and obesity prevalence in national studies were 5.0-13.5 (95% CI: 4.5-5.5, 13.4-13.6), and 3.2-11.9

Acta Medica Iranica 2015. 53(10):596-607.

Investigation of the Prevalence of Obesity in Iran: a Systematic Review and Meta-Analysis Study

Asghar Rahmani, Kourosh Sayehmiri, Khairollah Asadollahi, Diana Sarokhani, Farhad Islami, Mandana Sarokhani

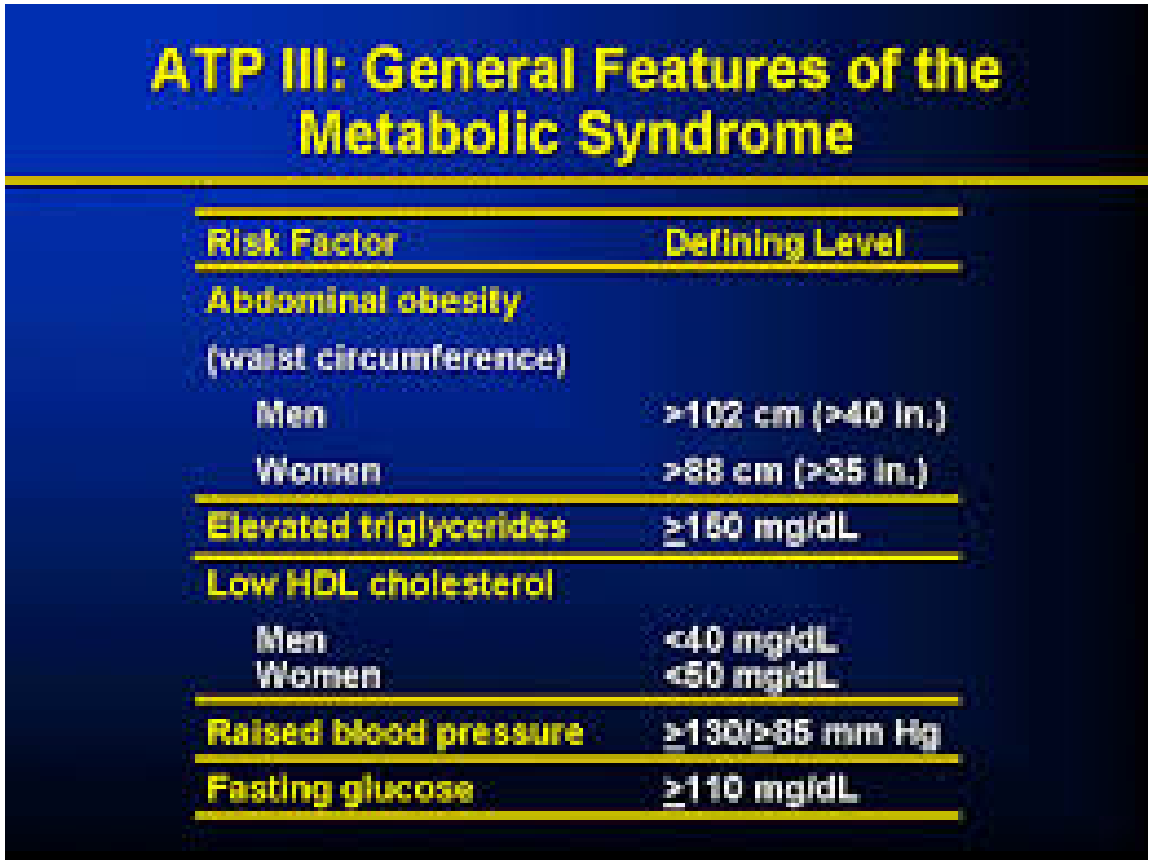
- A total of 144 articles with the sample size of 377858 people (134588 males and 164858 females) were enrolled in the study.
- The prevalence of obesity in populations above the age of 18 was estimated as 21.7% (CI 95%: 18.5% - 25%) and in populations below 18 as 6.1% (CI 95%: 6.8%-5.4%).
- Meta-regression analysis showed an ascending trend in the prevalence of obesity in Iran

Estimating the Prevalence and Trends of Obesity in Iran Populations from 2000 to 2011: A Meta-Analysis Study

Hossein Fallahzadeh1, Hasan Saadati, Naeimeh Keyghobadi

- The results showed that the prevalence of overweight and obesity have increased between 2000 to 2005 and 2006 to 2010; and from 2011 to 2013, this trend has decreased
- the prevalence of obesity and overweight was greater in persons over 18 years than under 18 years in all three time

METABOLIC SYNDROME



An obese man is about twice as likely to be infertile as a normal man

Human Reproduction, Vol.29, No.2 pp. 193–200, 2014
Advanced Access publication on December 4, 2013 doi:10.1093/humrep/det428

human reproduction ORIGINAL ARTICLE *Andrology*

The relationship between male BMI and waist circumference on semen quality: data from the LIFE study

- A linear association between increasing BMI and the incidence of oligospermia.
- Six percent of men with a normal BMI were oligospermic compared to 17% of obese men.
- Waist circumference was also correlated with low sperm concentration and low total sperm count
- Other studies have demonstrated similar associations between obesity and decreased sperm quantity

Human Reproduction Update, Vol.19, No.3 pp. 221–231, 2013
Advanced Access publication on December 12, 2012 doi:10.1093/humupd/dms050

human reproduction update

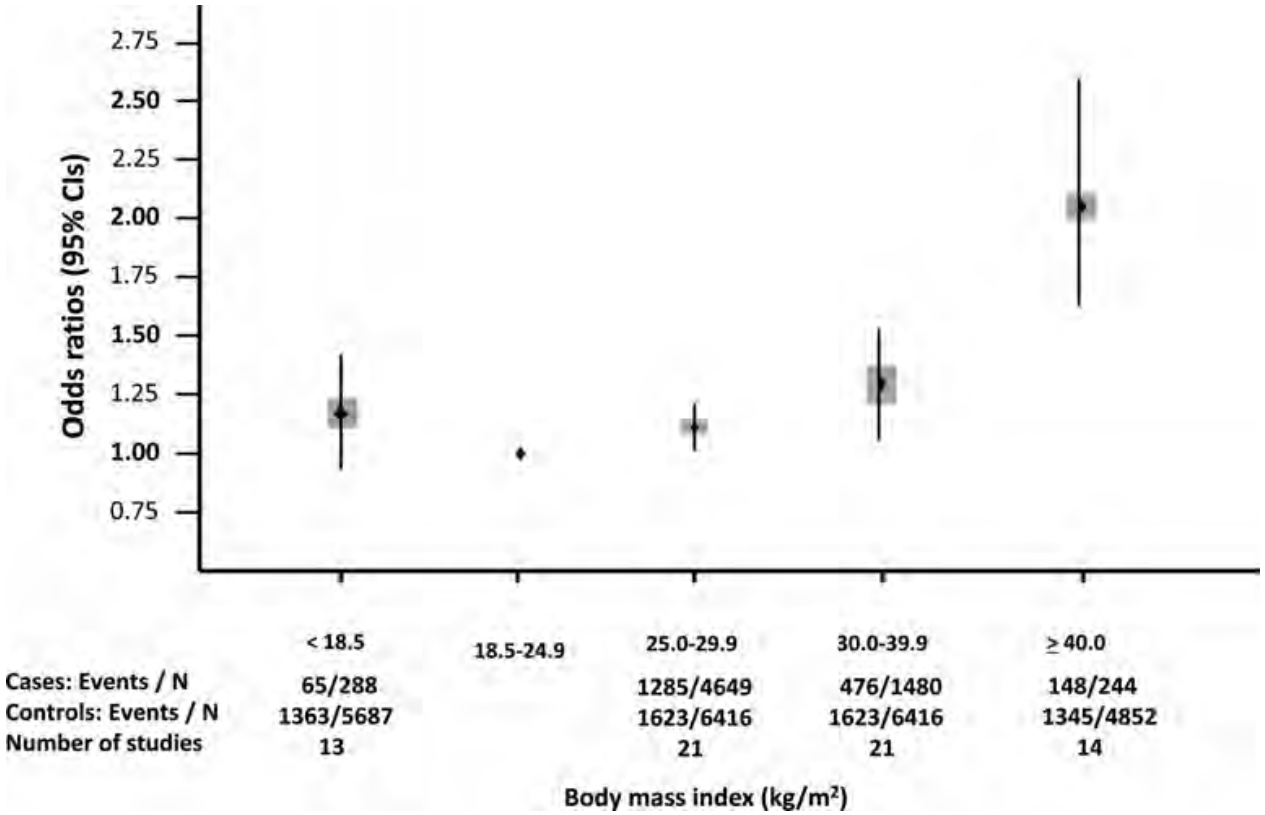
BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis

- A total of 21 studies were included in the meta-analysis, resulting in a sample of 13 077 men from the general population and attending fertility clinics.
- Standardized weighted mean differences in sperm concentration did not differ significantly across BMI categories.
- There was a J-shaped relationship between BMI categories and risk of oligozoospermia or azoospermia.
- Compared with men of normal weight, the odds ratio (95% confidence interval) for oligozoospermia or azoospermia was 1.15 (0.93–1.43) for underweight, 1.11 (1.01–1.21) for overweight, 1.28 (1.06–1.55) for obese and 2.04 (1.59–2.62) for morbidly obese men.
- Overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia

Human Reproduction Update, Vol.19, No.3 pp. 221–231, 2013
Advanced Access publication on December 12, 2012 doi:10.1093/humupd/dms050

human reproduction update

BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis



,36 Issue segaP ,2018 lirpA ,4Review

Effect of male body mass index on assisted reproduction treatment outcome: an updated systematic review and meta-analysis

Author links open overlay panelRabiaMushtaq[a]JyotsnaPundir[b]ChiaraAchilli[c]OsamaNaji[a]YacoubKhalaf[a]TarekEl-Toukhy[a]

- An electronic search for published literature was conducted in *MEDLINE* and *EMBASE* between 1966 and November 2016.
- Outcome measures were clinical pregnancy rates (CPR) and live birth rates (LBR) per IVF or ICSI cycle.
- Eleven studies were identified, including 14,372 cycles; nine reported CPR and seven reported LBR.
- Pooling of data from those studies revealed that raised male BMI was associated with a significant reduction in CPR (OR 0.78, 95% CI 0.63 to 0.98, P = 0.03) and LBR (OR 0.88, 95% CI 0.82 to 0.95, P = 0.001) per IVF–ICSI treatment cycle.
- Male BMI could be an important factor influencing IVF–ICSI outcome

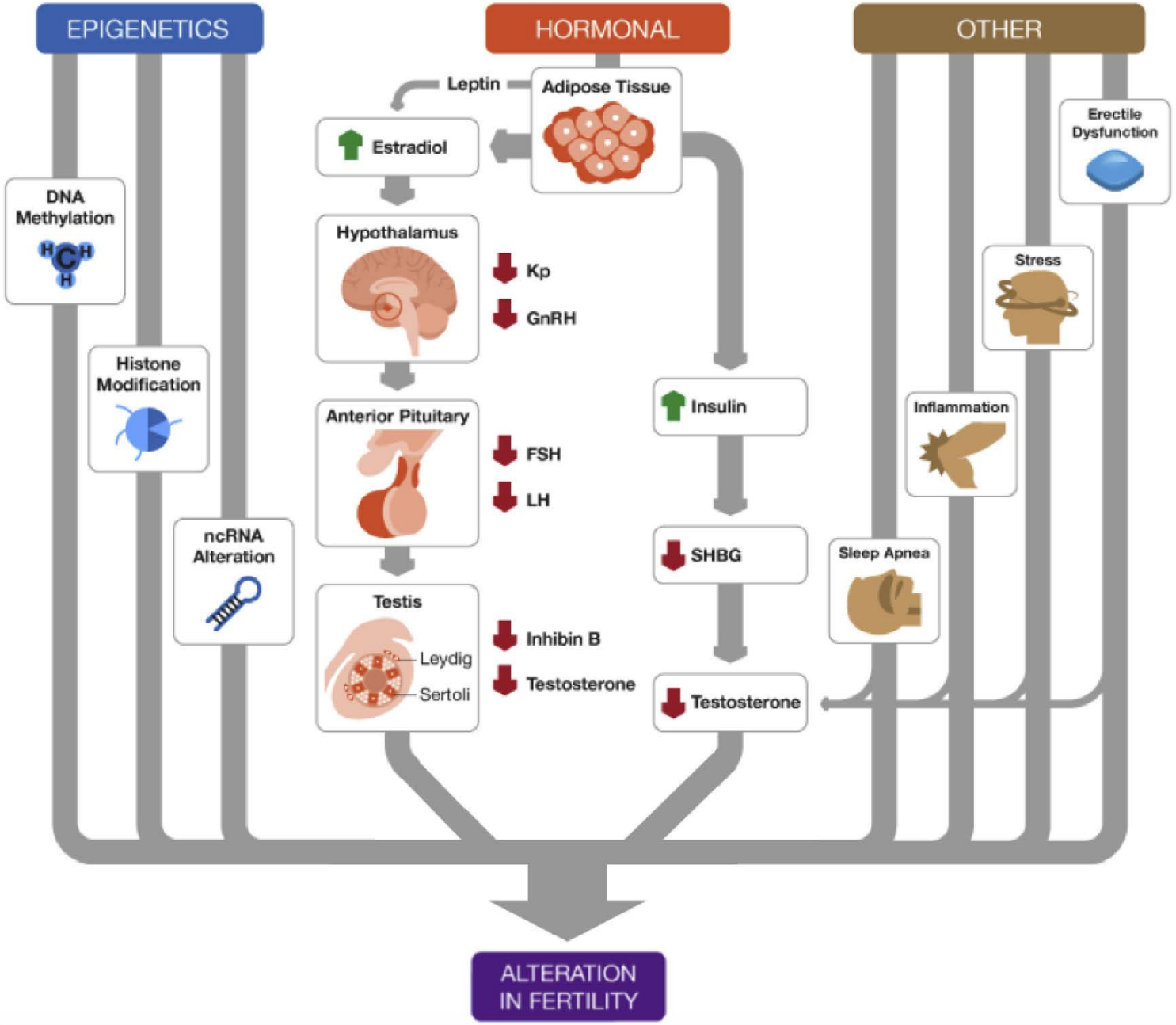
Reproductive BioMedicine Online (2015) **31**, 593–604

Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis

Jared M Campbell a,*, Michelle Lane b, Julie A Owens c, Hassan W Bakos

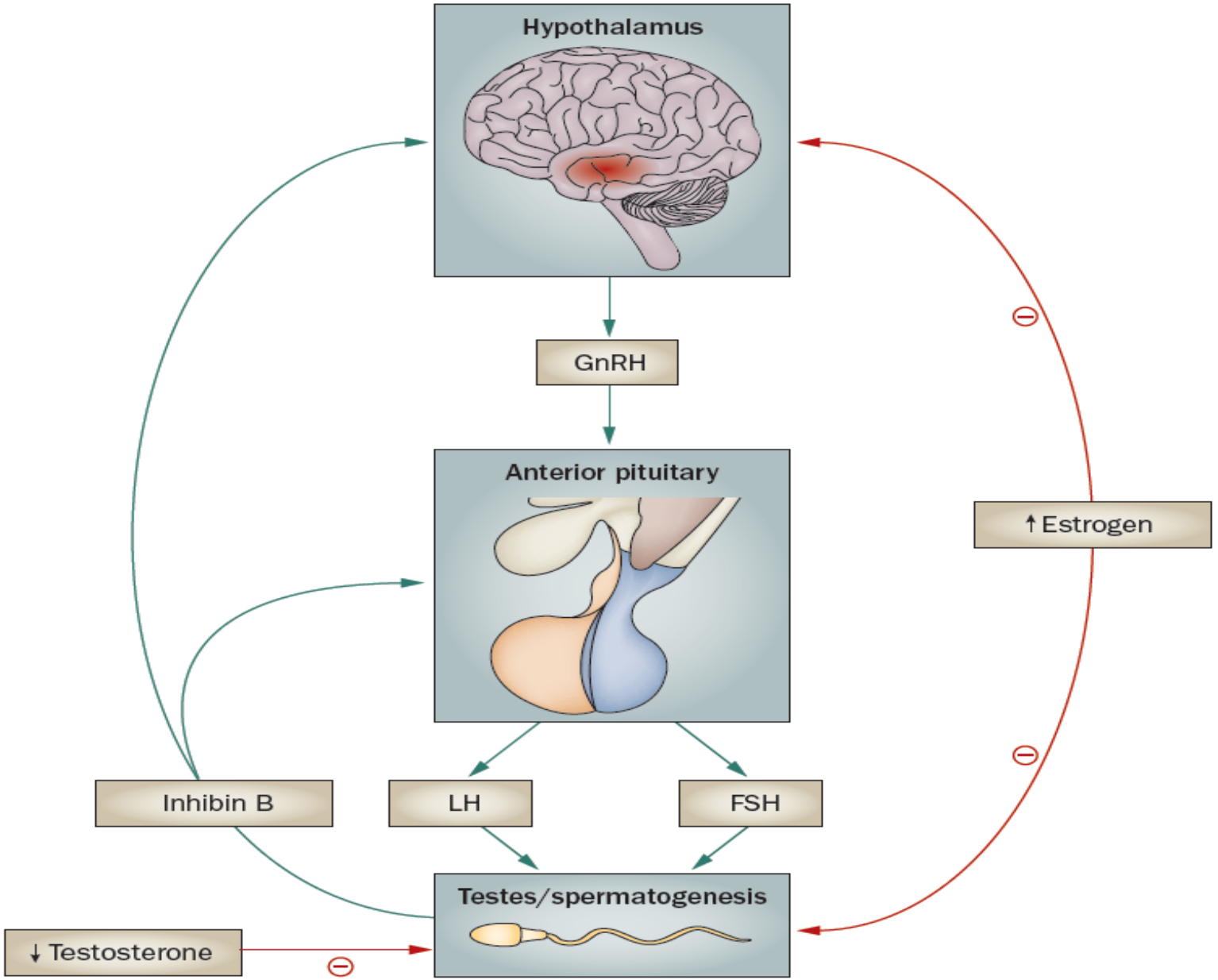
- Thirty papers were included, with a total participant number of 115,158.
- Obese men were more likely to experience infertility (OR = 1.66, 95% CI 1.53–1.79), their rate of live birth per cycle of assisted reproduction technology (ART) was reduced (OR = 0.65, 95% CI 0.44–0.97) and they had a 10% absolute risk increase of pregnancy non-viability.
- obese men had an increased percentage of sperm with low MMP, DNA fragmentation, and abnormal morphology.
- Clinically significant differences were not found for conventional semen parameters.
- From these findings it can be concluded that male obesity is associated with reduced reproductive potential

Obesity and Male Infertility: Potential Mechanisms



Obesity leads to hypogonadism

- Most obese males have altered reproductive hormonal profiles, e.g. elevated estrogen and leptin levels, and decreased testosterone, follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), ghrelin and inhibin B levels
- the low testosterone and FSH levels in obese men can be a cause for impaired spermatogenesis and finally lead to reduced sperm counts and subfertility


Hypothalamus
GnRH
Anterior pituitary
↑ Estrogen
Inhibin B
LH
FSH
Testes/spermatogenesis
↓ Testosterone

Obesity induces inflammation

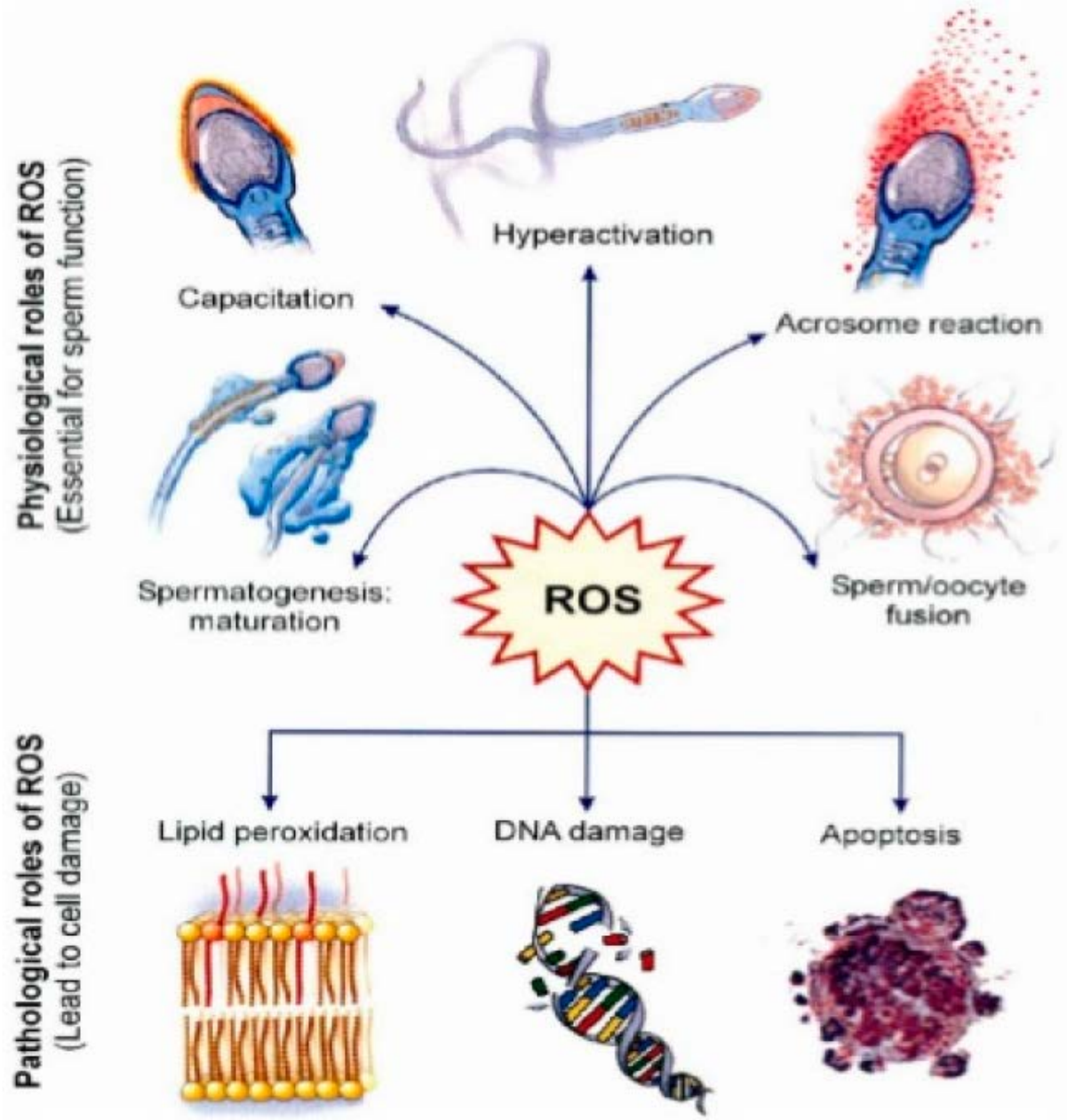
- pro-inflammatory cytokines, such as TNF-α and IL-6, are also increased in the serum, testicular tissue and the seminal plasma of obese males
- pro-inflammatory cytokines exert some impacts on the HPG axis and on fertility
- In testis, pro-inflammatory cytokines can directly impair the seminiferous epithelium
- Pro-inflammatory state induced by obesity can also damage epididymal epithelium function, by altering the environment within the epididymis, modifying the epididymosomes content and increasing the influx of neutrophils and macrophages to the epididymial lumen, resulting in higher cytokine expression and epithelial apoptosis, thus impeding sperm maturation and fertilization ability.

Obesity enhances oxidative stress

- One of the main factors relevant to disrupted sperm function in obese males is the oxidative stress caused by excess of reactive oxygen species (ROS), mainly including superoxide anion, nitric oxide, hydroxyl radical and oxidants
- Obesity, associated with the chronic inflammatory state, causes a higher metabolic rate and an increased ROS formation in testicular tissue, reproductive tract and semen
- Several studies have shown that oxidative stress in semen and testis were positive correlations to the increase in BMI and sperm DNA damage, and negative correlation to the decreased sperm motility and acrosome reaction

Obesity enhances oxidative stress

- in obese male, increased scrotal adiposity directly leads to increases in gonadal heat
- Definitely, increased testicular heat can substantially reduce sperm motility and concentration and increase sperm DNA damage and sperm oxidative stress as well
- a positive correlation exists between increasing BMI and higher sperm/seminal plasma ROS levels


Physiological roles of ROS
(Essential for sperm function)
Capacitation
Hyperactivation
Acrosome reaction
Spermatogenesis: maturation
ROS
Sperm/oocyte fusion
Pathological roles of ROS
(Lead to cell damage)
Lipid peroxidation
DNA damage
Apoptosis

Andrologia. 2011 Apr;43(2):121-8. doi: 10.1111/j.1439-0272.2009.01032.x. Epub 2010 Dec 29.

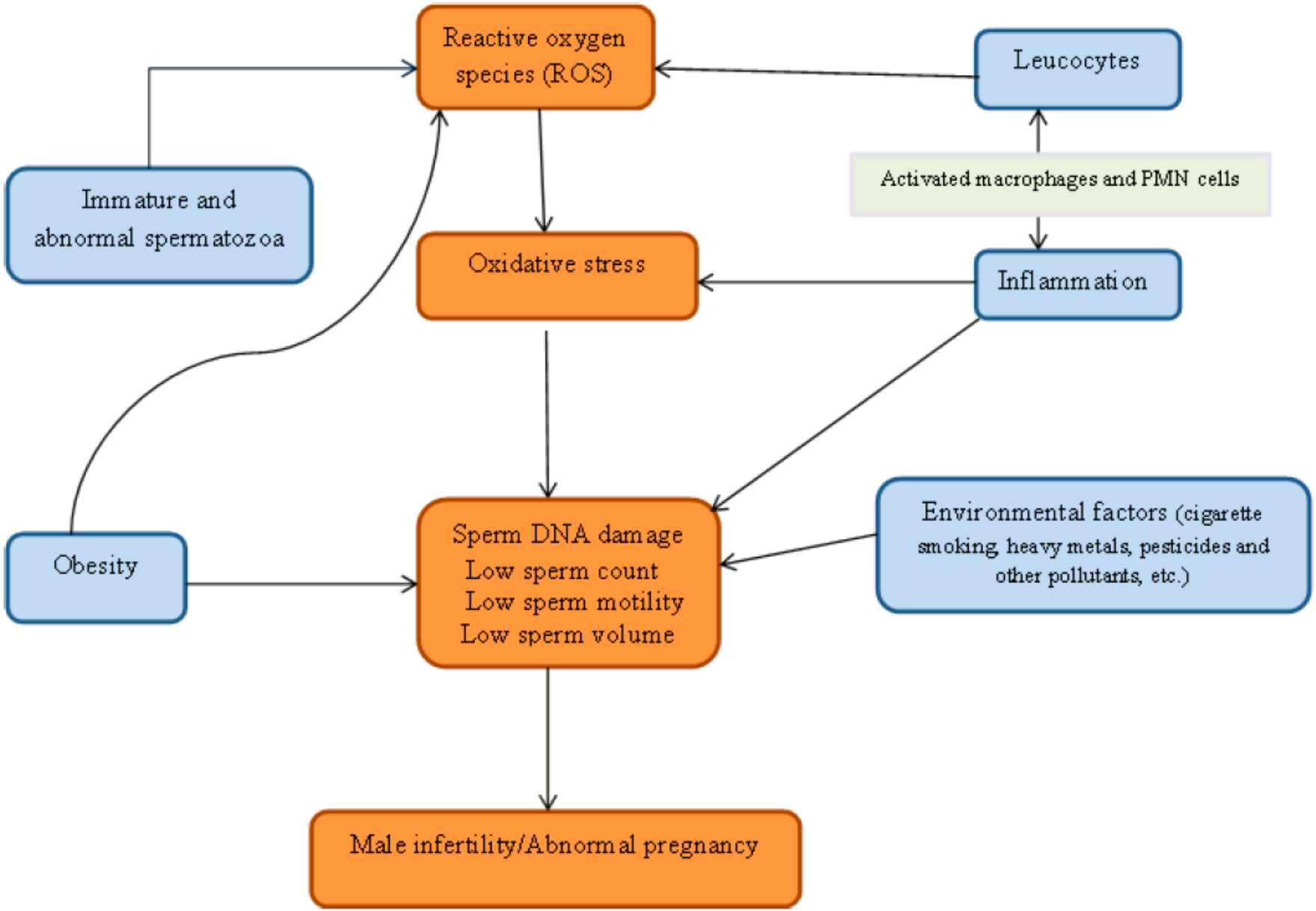
Impact of body mass index on seminal oxidative stress.

Tunc O, Bakos HW, Tremellen K.

- The primary aim of this study was to determine if sperm oxidative stress was more common in obese/overweight men.
- A total of 81 men had their body mass index (BMI) correlated with seminal reactive oxygen species (ROS) production (Nitro Blue Tetrazolium assay), sperm DNA damage (TUNEL), markers of semen inflammation (CD45, seminal plasma PMN elastase and neopterin concentration) and routine sperm parameters, together with reproductive hormones.
- The principal finding from this study was that oxidative stress did increase with an increase in BMI, primarily due to an increase in seminal macrophage activation.

Obesity impairs sperm parameters

- The effect of male obesity on sperm parameters, such as sperm concentration, sperm motility and morphology, has been well documented in human and animal models
- many factors altered in obese male may impair sperm quality including sexual hormone imbalance, oxidative stress and chronic inflammation.


Reactive oxygen species (ROS)
Leucocytes
Immature and abnormal spermatozoa
Activated macrophages and PMN cells
Oxidative stress
Inflammation
Obesity
Sperm DNA damage
Low sperm count
Low sperm motility
Low sperm volume
Environmental factors (cigarette smoking, heavy metals, pesticides and other pollutants, etc.)
Male infertility/Abnormal pregnancy

Obesity increases sperm DNA damage

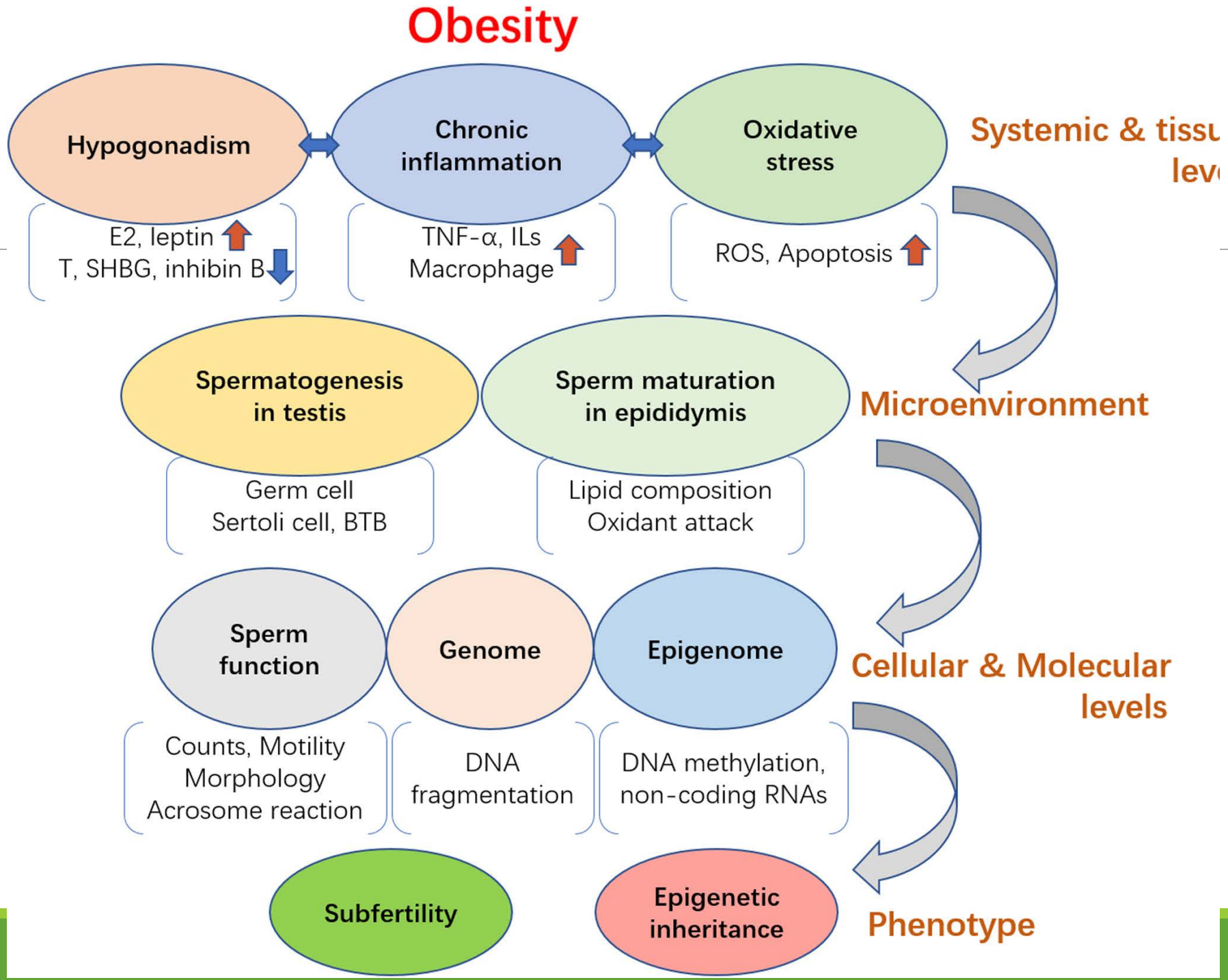
- The integrity of DNA in the sperm nucleus is an important determinant of semen quality since it is vital for fertilization rates, embryo quality, pregnancy rates and miscarriage rates as well
- There are numerous human and animal studies to show the significant negative associations between obesity and sperm DNA integrity
- One of the main contributors in obesity for sperm DNA structure damage is ROS
- because of the limitation in antioxidant defensive capacity and defectiveness in DNA repair system, the DNA damage induced by ROS in spermatozoa is particularly crippling and increases the risk of failure in further fertilization and embryonic development

Obesity alters sperm lipid composition

- The sperm membrane is composed of various saturated fatty acids (i.e. myristic acid, palmitic acid, stearic acid etc.) and unsaturated fatty acids (i.e. palmitoleic acid, oleic acid, linoleic acid, arachidonic acid, docosahexaenoic acid etc.).
- The fatty acid composition of spermatozoa is important for the sperm function, including sperm motility, viability and fertility
- changes in the fatty acid composition of spermatozoa could be one of the mechanisms underlying reduced sperm quality in men with high BMI

Obesity influences sperm epigenetic modification

- Epigenetic modifications, such as DNA methylation and hydroxymethylation, histone modifications and non-coding RNA expression, modulate the transcription intensity and regulate gene expression in time and space without altering the genetic information in DNA
- recent studies on epigenetic modifications influenced by obesity demonstrate that alterations in DNA methylation are a consequence of increased BMI
- some clinical and animal studies suggest that paternal obesity may also have an impact on the metabolic health for his and/or her offspring and grand-offspring, which means that children born from obese parents are more likely to develop childhood obesity and suffer from adverse metabolic diseases


Obesity
Hypogonadism
Chronic inflammation
Oxidative stress
Systemic & tissu
lev
E2, leptin
T, SHBG, inhibin B
TNF-α, ILs
Macrophage
ROS, Apoptosis
Spermatogenesis in testis
Sperm maturation in epididymis
Microenvironment
Germ cell
Sertoli cell, BTB
Lipid composition
Oxidant attack
Sperm function
Genome
Epigenome
Cellular & Molecular levels
Counts, Motility
Morphology
Acrosome reaction
DNA fragmentation
DNA methylation, non-coding RNAs
Subfertility
Epigenetic inheritance
Phenotype

TREATMENT MODALITIES

LIFE-STYLE AND NUTRITIONAL CHANGES

- Diet
- Exercise

PHARMACOLOGICAL INTERVENTION

- Appetite Suppressors (sibutramine)
- Weight Loss Drugs (orlistat)
- Aromatase Inhibitors (anastrazole, letrozole)

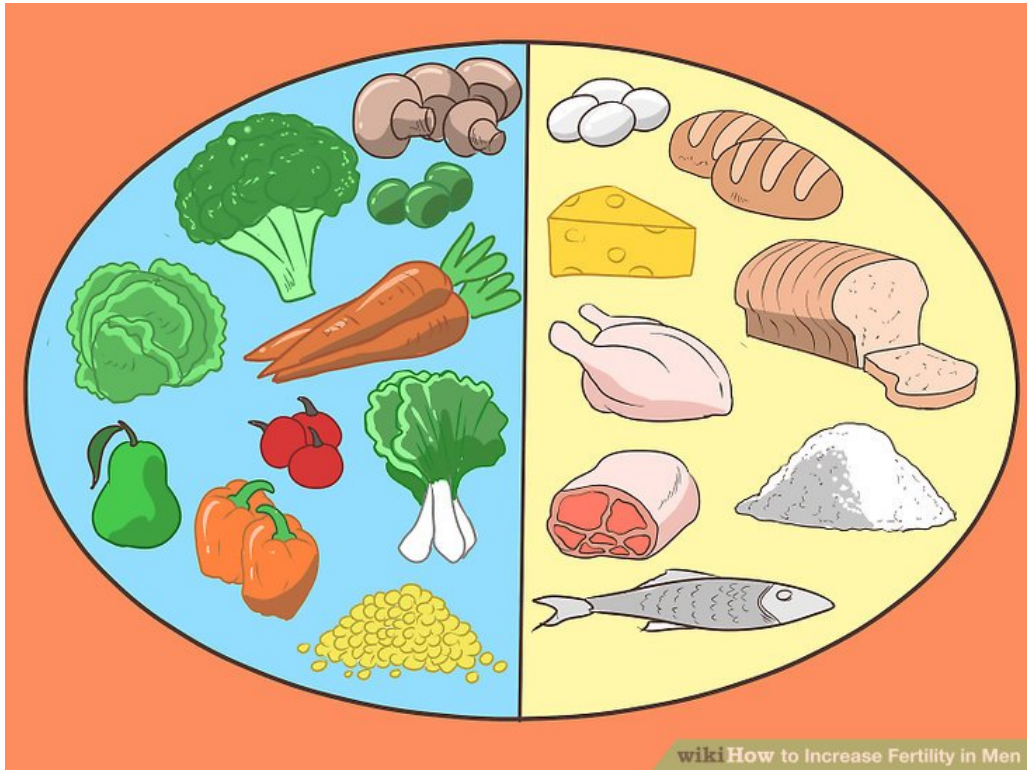
SURGICAL INTERVENTION

- Bariatric Surgery
- Scrotal Lipectomy

ART

- IUI
- IVF
- ICSI

Maintaining a Healthy Lifestyle



Eat a healthy diet

The various nutritional factors that have negative effects on male/female fertility

Trans fatty acids	High intake of trans fatty acids cause significant decline in sperm concentration and sperm count.
	Trans fatty acids play a negative role in reproduction by increasing risk of ovulatory infertility in women with polycystic ovary syndrome.
	Trans fatty acids demonstrate positive correlation with asthenospermia.

The various nutritional factors that have negative effects on male/female fertility

Alcohol	Alcohol consumption reduces the fertilization rate and negatively affects fecundability.
	Moderate alcohol consumption positively affects levels of serum testosterone and does not harm semen quality.
	Alcohol consumption found to be related to low sperm volume and high sperm DNA fragmentation. İnfertile men who drink alcoholic beverages 2–3 units per day have worse semen quality compared with occasional drinkers (<3 units per week).
	Alcohol consumption is associatied with deterioration of most semen properties.
	The intake of the modest alcohol (5 units in a week) negatively affect semen quality.
	Alcohol consumption increases the numbers of morphologically abnormal sperm.

The various nutritional factors that have negative effects on male/female fertility

Red meat and processed meat	Processed meat is the risk factor of asthenozoospermia.
	Processed meat is associated with lower sperm count and lower progressive motile sperm and abnormal sperm morphology.
	The consumption of red meat is associated with a greater rate of ovulatory disorder infertility. Frequent intake of meat products may adversely affect semen quality.
	Semen parameters may be enhanced by diets which include restricted processed meats and cheese.
	Sausage and turkey ham intake may adversely affect assisted reproductive parameters.
Sugars	Sugar decreases sperm motility.

The various nutritional factors that have negative effects on male/female fertility

Soy foods	A higher intake of soy foods may decrease sperm concentration.
	The consumption of soy (0.30 serving/day) increases the risk of infertility in males.
Dairy products	The consumption of whole-fat dairy products decreases to sperm motility and negatively alters the sperm morphology.
	Higher dairy protein intake (≥5.24% of energy) of women treated with infertility is associated with lower antral follicle counts.
Caffeine	The live birth rate of couples which male partner consume caffeine ≥ 272 mg/day is approximately 3 times lower than couples which male partner consume caffeine <99 mg/day.
Coffee	Pre-pregnancy coffee consumption (≥4 servings/day) increases risk of spontaneous abortion especially at weeks 8–19. There is no spontaneous abortion relation of caffeinated tea and caffeinated soda.

The various nutritional factors that have negative effects on male/female fertility

Lacto-ovo vegetarian diet and vegan diet	Vegetables-based food intake decreases sperm quality.
	The sperm concentration of lacto-ovo vegetarians was found significantly lower than non-vegetarians.
	Total sperm motility was found lower in the lacto-ovo and vegan groups than non-vegetarians. Vegans had lowest hyperactive motility.
Genetically modified food/organism	Genetically modified food/organism can be potential risk on reproduction, through influencing the endocrine metabolism.

The various nutritional factors that have negative effects on male/female fertility

Fat and fatty acids and energy and carbohydrates	While saturated fatty acids, monounsaturated fatty acids, energy derived from fat have statistically significant positive correlation with immotiliy where as there is a statistically negative correlation between the energy value of the diet and sperm concentration.
	Energy derived from the carbohydrates is associated with lower semen volume, consistency.
	The energy derived from fat is associated with lower sperm consistency and immotility.
	Total fat intake increases testosterone concentrations in healthy women in a very small way and it is inversely associated with the high embryo quality rate.

The various nutritional factors that have positive effects on male/female fertility

Mediterranean diet	Persistence of the Mediterranean diet (characterized by high intakes of vegetables, fruits and seafood) support the higher sperm concentration and total sperm count and sperm motility.
Poultry	Inadequate intake of poultry was associated with a significantly higher risk of asthenozoospermia. Therefore, intake of poultry decreases the risk of asthenozoospermia.
	Poultry intake was positively associated with fertilization rates and supports fecundability.
Fish	Semen parameters may be enhanced by a rich diet from fish.
	Fish intake positively affects total sperm count and sperm morphology.

The various nutritional factors that have positive effects on male/female fertility

Fruits and vegetables	Daily intake of citrus fruits which are high in beta-cryptoxanthin (≥ 1 servings) decreases risk of endometriosis (aproximately 22%) compared to consuming less than 1 per week.
	Daily intake of cruciferous vegetables (≥1 servings) has a 13% higher risk of endometriosis compared to those consuming less than 1 per week.
	The consumption of fruit is positively associated with sperm motility.
	Fruits or vegetables may maintain or improve semen quality.
	Low intake of fruits and vegetables (<5 serving/day) increases the risk of infertility in males.
Lycopene	Lycopene positively affects sperm morphology
Low-fat dairy products	It is associated with a higher sperm concentration and progressive motility.
	Semen parameters may be improved by consumption of low-fat dairy.

The various nutritional factors that have positive effects on male/female fertility

Whole grain	Higher intake of whole grain includes specific nutrients such as phytic acid, vitamin E, and selenium at pre-treatment period was related to higher probability of live birth among women undergoing in vitro fertilization.
	The consumption of cereals is positively associated with sperm motility.
Omega-3	Proven fertile men have higher concentrations of omega-3 fatty acids in blood and spermatozoa than infertile men.
Prudent diet (contains high consumption of fish, poultry, fruit, vegetables, legumes and whole grains)	There is a positive correlation between prudent pattern and the percentage of progressively motile sperm but no strong correlation between prudent pattern and sperm concentration and morphology.

Regular exercise

Håkonsen et al. Reproductive Health 2011, 8:24
http://www.reproductive-health-journal.com/content/8/1/24

REPRODUCTIVE HEALTH

RESEARCH Open Access

Does weight loss improve semen quality and reproductive hormones? results from a cohort of severely obese men

- 43 men with BMI > 33 kg/m2 were followed through a 14 week residential weight loss program
- Weight loss was associated with an increase in total sperm count (p = 0.02), semen volume (p = 0.04), testosterone (p = 0.02), SHBG (p = 0.03) and AMH (p = 0.02).
- The group with the largest weight loss had a statistically significant increase in total sperm count [193 millions (95% CI: 45; 341)] and normal sperm morphology [4% (95% CI: 1; 7)].

10.5005/jp-journals-10016-1136

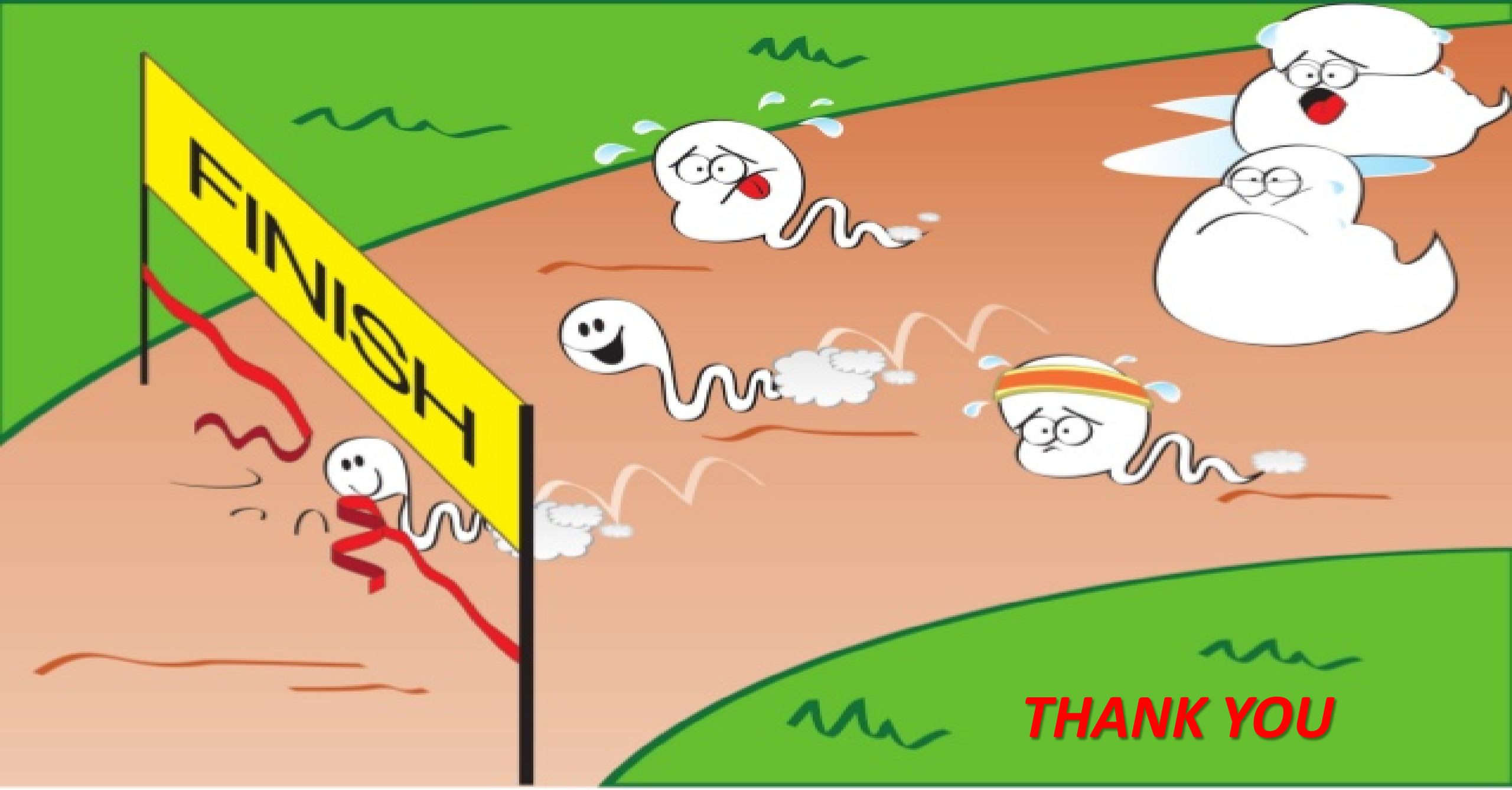
ORIGINAL RESEARCH

Does Weight Loss improve Fertility with Respect to Semen Parameters? Results from a Large Cohort Study

- All men attending infertility center from April 2012 to May 2015 (n = 105).
- The mean BMI was significantly higher before weight loss (33.2) than after weight loss (30.4) in obese men.
- The weight loss had significant positive correlation with percentage of progressive sperm motility ($p = 0.001$) and static percentage ($p \leq 0.001$)
- In one of the largest cohorts of male fertility and obesity, semen parameters demonstrated mild but significant relationships with BMI and semen parameters, possibly contributing to subfertility in this population

Take-home Messages

- ✓ Obesity is a risk factor for male infertility
- ✓ Obese men have lower sperm count,as well as increased sperm DNA damage and oxidative stress
- ✓ Peripheral androgen aromatization is often increased in obese men thus affecting HPG axis. Other mechanisms involve physical, genetic and adipocyte-secreted factors
- ✓ The role of interventions to restore fertility of obese men is yet to be fully characterized


FINISH
THANK YOU