26° Congresso Interassociativo SID-AMD Lombardia 2020

# Diabete

# La disfunzione della sfera sessuale nell'uomo

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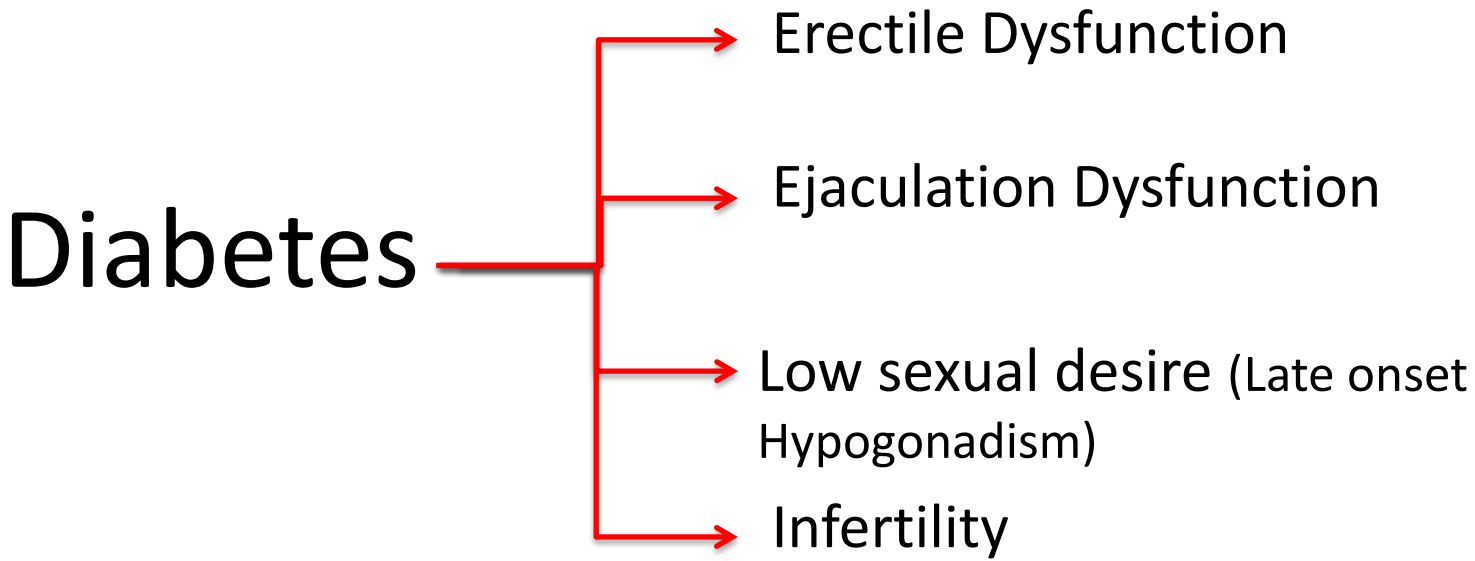
# Diabetes & Sexual Dysfunctions



# Erectile Dysfunction

## 3.1 Erectile dysfunction

### *3.1.1 Epidemiology/aetiology/pathophysiology*

Penile erection is a complex phenomenon which implies a delicate and co-ordinated equilibrium among the neurological, vascular and the smooth muscle compartment. It includes arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [26]. Erectile Dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [27]. Erectile Dysfunction may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partner's [28-30]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. Erectile Dysfunction should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD) [31-33].

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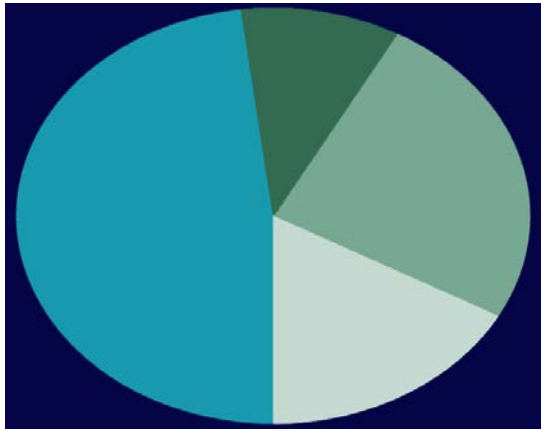
# Erectile Dysfunction - Epidemiology

## ED is highly prevalent

**Men aged 40 to 70 years**



**Massachusetts Male Aging Study (n=1290)**

**ED (52%)**

- **Complete (10%)**
- **Moderate (25%)**
- **Minimal (17%)**

**No ED (48%)**

Feldman HA, et al. J Urol , 151:54-61, 1994

# Erectile Dysfunction - Pathophysiology

| Hormonal |
| --- |
| Diabetes Mellitus; Metabolic Syndrome; |
| Hypogonadism (any type) |
| Hyperprolactinaemia |
| Hyper- and hypothyroidism |
| Hyper- and hypocortisolism (Cushing's disease, etc.) |
| Panhypopituitarism and multiple endocrine disorders |

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# Erectile Dysfunction & Diabetes

Vasculogenic

| |
|---|
| **Vasculogenic** |
| • Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.) |
| • Diabetes mellitus |
| • Hyperlipidaemia |
| • Smoking |
| • Major pelvic surgery (RP) or radiotherapy (pelvis or retroperitoneum) |
| **Neurogenic** |
| *Central causes* |
| • Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.) |
| • Spinal cord trauma or diseases |
| • Stroke |
| • Central nervous system tumou |
| *Peripheral causes* |
| • Type 1 and 2 diabetes mellitus |
| • Chronic renal failure |
| • Polyneuropathy |
| • Surgery (major surgery of pelvis/retroperitoneum, radical prostatectomy (RP), colorectal surgery, etc.) |
| • Surgery of the urethra (urethral stricture, urethroplasty, etc.) |
| **Anatomical or structural** |
| • Hypospadias, epispadias |
| • Micropenis |
| • Peyronie's disease |
| • Penile cancer |
| • Phimosis |
| **Hormonal** |
| • Hypogonadism |
| • Hyperprolactinaemia |
| • Hyper- and hypothyroidism |
| • Hyper- and hypocortisolism (Cushing's disease, etc.) |
| • Panhypopituitarism and multiple endocrine disorders |
| **Drug-induced** |
| • Antihypertensives (thiazide diuretics, etc.) |
| • Antidepressants (selective serotonin reuptake inhibitors, tricyclics) |
| • Antipsychotics (neuroleptics, etc.) |
| • Antiandrogens (GnRH analogues and antagonists) |
| • Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, etc.) |
| **Psychogenic** |
| • Generalised type (e.g., lack of arousability and disorders of sexual intimacy) |
| • Situational type (e.g., partner-related, performance-related issues or due to distress) |
| **Trauma** |
| • Penile fracture |
| • Pelvic fractures |

Peripheral (neurogenic)

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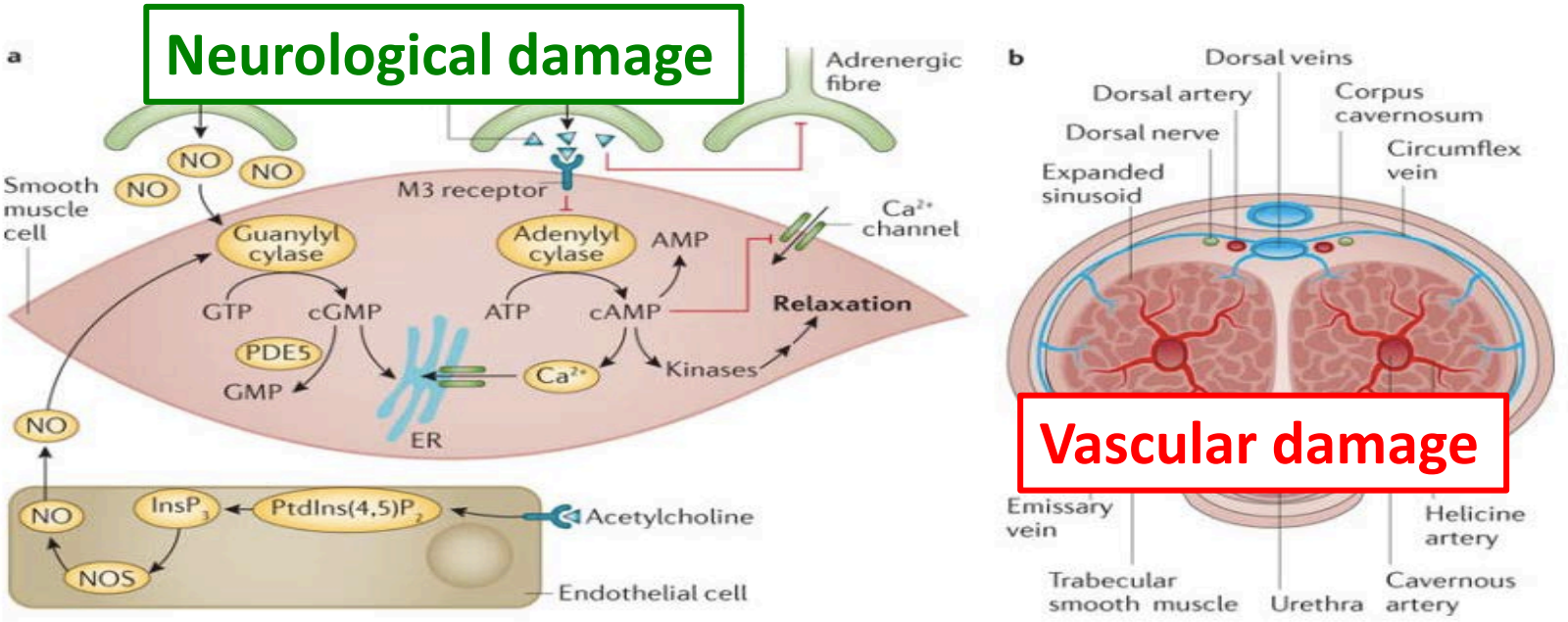
# Erectile Dysfunction & Diabetes



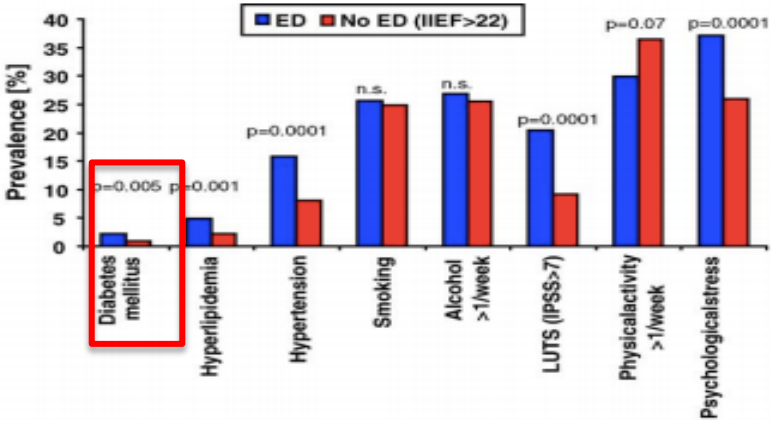
# High prevalence of erectile dysfunction in diabetes:

# A systematic review and meta-analysis of 145 studies

| Outcome | Number of study estimates | Number of participants | Prevalence (%) | 95% CI | | Between group p value | $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| **ED (main analysis)** | **145** | **88,577** | **59.1** | **55.5** | **62.7** | **-** | **99** |
| **Continent** | | | | | | *<0.0001* | |
| *Africa* | *15* | *2,055* | ***71.3*** | *63.2* | *78.2* | | *92* |
| *Asia* | *61* | *36,032* | ***67.0*** | *60.4* | *73.1* | | *99* |
| *Europe* | *48* | *3,7300* | ***53.6*** | *48.7* | *58.3* | | *99* |
| *North America* | *17* | *10,509* | ***34.5*** | *26.1* | *44.0* | | *99* |
| *South America* | *1* | *114* | ***74.6*** | *65.8* | *81.7* | | *-* |
| *Oceania* | *1* | *788* | ***74.4*** | *71.2* | *77.3* | | *-* |
| *Multi-continent* | *2* | *1,779* | ***39.7*** | *37.5* | *42.0* | | *0* |

**Kouidrat et al. Diabet Med 2017 Sep;34(9):1185-1192**

# Erectile Dysfunction & Diabetes




Odds ratios (plus 95% confidence intervals) for the presence of ED

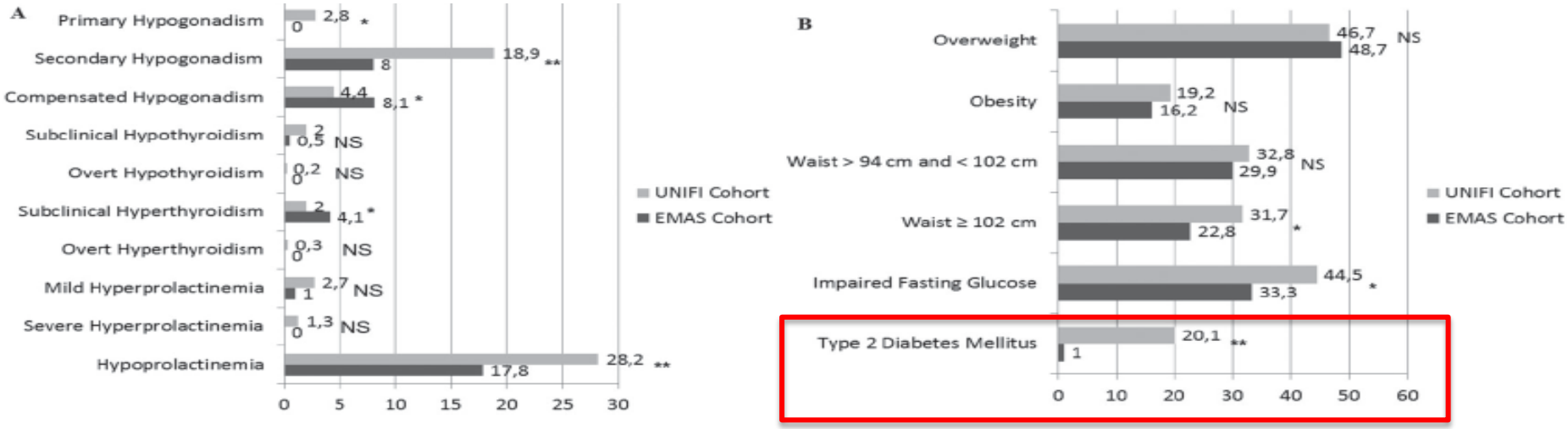
| | Total | 41–50 years | 51–60 years | 61–70 years |
|---|---|---|---|---|
| Referent | 20–30 years | | | |
| 41–50 years | 1.28 (0.98–1.7) | | | |
| 51–60 years | 1.7 (1.28–2.27) | | | |
| 61–70 years | 3.32 (2.34–4.71) | | | |
| Physical activity (</>1/week) | 1.35 (1.15–1.6) | 1.51 (1.1–2.0) | 2.04 (1.4–2.9) | 1.53 (0.88–2.6) |
| Psychological stress (yes/no) | 1.68 (1.43–1.98) | 1.36 (0.97–1.9) | 1.1 (0.75–1.52) | 1.28 (0.65–2.5) |
| Hypertension (yes/no) | 2.05 (1.61–2.6) | 1.46 (0.9–2.4) | 1.33 (0.88–2.0) | 1.75 (0.96–3.2) |
| DM (yes/no) | 3.0 (1.53–5.87) | 1.96 (0.55–7.0) | 2.0 (0.67–5.9) | 4.7 (0.58–37.8) |
| Hyperlipidemia (yes/no) | 2.29 (1.42–3.7) | 1.21 (0.56–2.6) | 1.16 (0.48–2.77) | 3.4 (1.1–10.6) |
| LUTS (IPSS≤/>7) | 2.2 (1.76–2.76) | 1.64 (1.06–2.5) | 2.07 (1.34–3.2) | 1.37 (0.72–2.6) |

**Diabetes represents undoubtedly one of the major risk factors for ED**

Ponholzer A et al, Eur Urol 2005; 47: 80-86

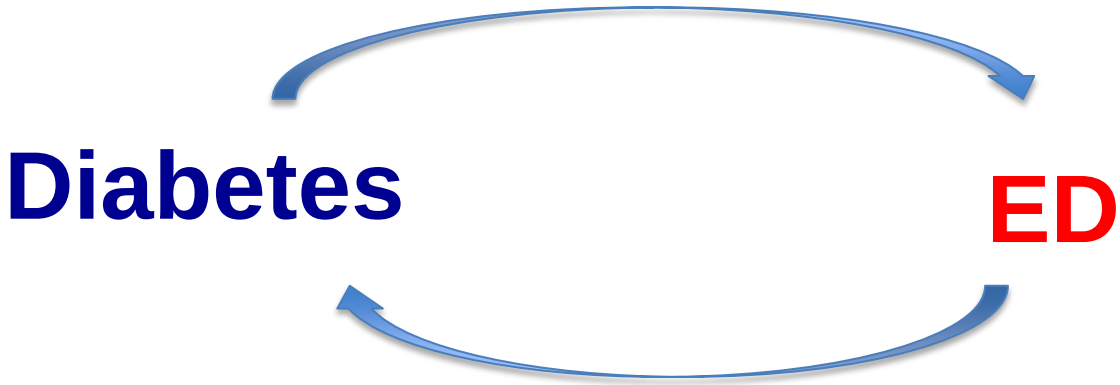
# Erectile Dysfunction & Diabetes

The **prevalence of endocrine abnormalities** was assessed in a general population sample (EMAS) and in a population of ED patients (UNIFI)




**T2DM, IFG, central obesity, are more frequent in subjects consulting for ED** than in the general population of the same geographic area

Maseroli E et al J Sex Med 2015


Diabetes
ED

# Erectile dysfunction may be the first clinical sign of insulin resistance and endothelial dysfunction in young men

**Table 2** Logistic regression analysis for the presence of ED in young men

| Variables | OR | 95 % CI | *p* value |
|---|---|---|---|
| FMD | 2.126 | 1.603–2.821 | <0.001 |
| SBP | 0.901 | 0.823–0.986 | 0.024 |
| HOMA | 0.005 | 0.000–0.079 | <0.001 |
| CHO | 0.357 | 0.138–0.918 | 0.033 |

**Young patients with ED had significantly higher levels of the insulin resistance-index (HOMA-IR)**, which has been previously associated to endothelial dysfunction and thus suggesting that **an early glycometabolic disorder may be an important mechanisms of organic ED in young patients**

**Yao et al. Clin Res Cardiol (2013) 102:645–651**

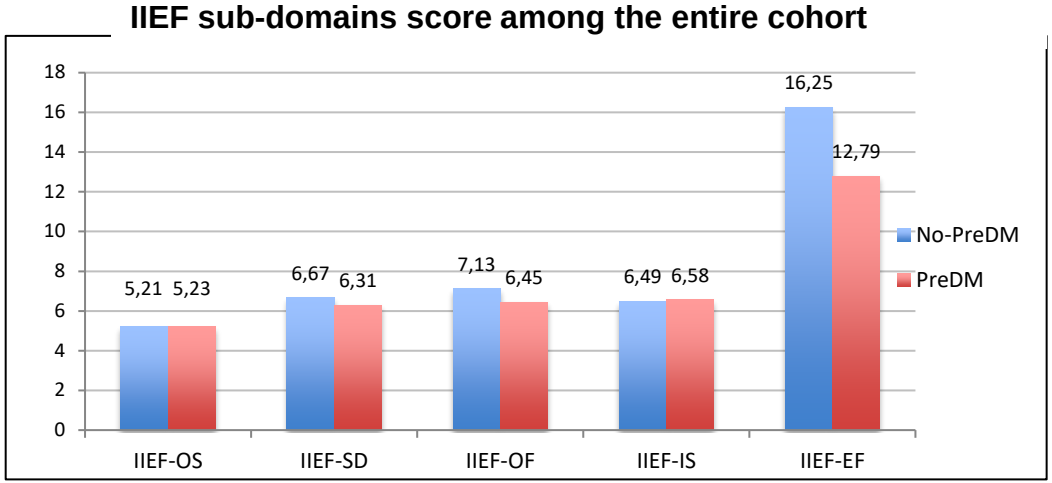
# Sexual Dysfunction In Men With Pre-diabetes
# Results From A Cross-sectional Study

Prediabetes (PreDM) was defined if:

**IFG: 100 - 125 mg/dL;**

**IGT from 140 mg/dL to 199 mg/dL**

**HbA1c values of 39 mmol/mol (5.7%) - 46 mmol/mol (6.4%)**




| | Severe ED (IIEF-EF 6-10) | |
|---|---|---|
| | Univariable analysis | Multivariable analysis |
| Age | 1.02 (<0.001) | 1.02 (0.01) |
| BMI | 0.99 (0.49) | 0.95 (0.06) |
| CCI | 1.38 (0.002) | 0.85 (0.3) |
| tT < 3 ng/m | 1.41 (0.103) | 1.47 (0.1) |
| Smoking status (Yes vs. No) | 1.21 (0.04) | 1.36 (0.3) |
| +PreDM | 2.31 (0.001) | 2.03 (0.02) |

**Boeri L et al. J Sex Med 2018**

- **One-out of five men** seeking medical help for new onset ED showed **glucose levels suggestive for PreDM status.**
- **Men with PreDM reported** a **greater risk of severe ED** compared to those without PreDM.
- This finding stigmatizes the **clinical relevance of a detailed metabolic and hormonal investigation in patients presenting with ED.**

# ED treatment in patients with DM

# PDE5is - efficacy

The efficacy of all PDE5 inhibitors is **clearly less in special ED subpopulations:**

- **RP**
- **DM**

in which either the autonomic parasympathetic innervation to the penis or the functional capacity of the cavernous bodies (venoocclusive dysfunction) is clearly impaired

**Table 8** Efficacy of the three PDE5 inhibitors in a variety of ED populations

| | Sildenafil/placebo (50/100 mg) | | Tadalafil/placebo (10/20 mg) | | | Vardenafil/placebo (10/20 mg) | | |
|---|---|---|---|---|---|---|---|---|
| ED population | GAQ (%) | SEP 2/3 (%) | GAQ (%) | SEP 2 (%) | SEP 3 (%) | GAQ (%) | SEP 2 (%) | SEP 3 (%) |
| Mixed | 82/24 (N = 1,600–1,787)* | 66/20 | 81/35 (N = 1,112)† | Not reported | 75/32 | 80/30 (N = 601)‡ | Not reported | 75/39 |
| | | | | | | 85/28 (N = 804)§ | 81/52 | 67/33 |
| Diabetes | 56/10 (N = 268)*,¶ | 48/12 | 64/25 (N = 216)** | 57/30 | 48/20 | 72/13 (N = 452)†† | 64/36 | 54/23 |
| BNSP RRP | No controlled multicenter studies | | 62/23 (N = 303)‡‡ | 54/32 | 41/19 | 65/13 (N = 427)§§ | 48/22 | 37/10 |

**Porst H et al. J Sex Med 2013**

# PDE5is – management of nonresponders

## Improvement of related comorbid conditions

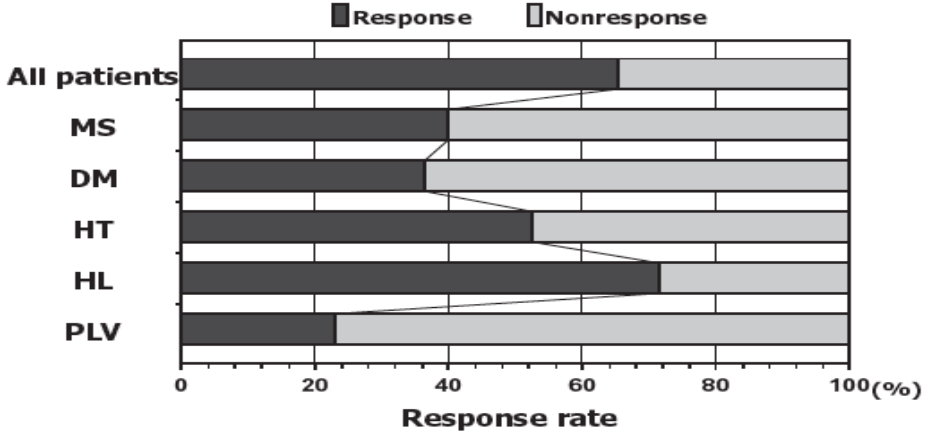
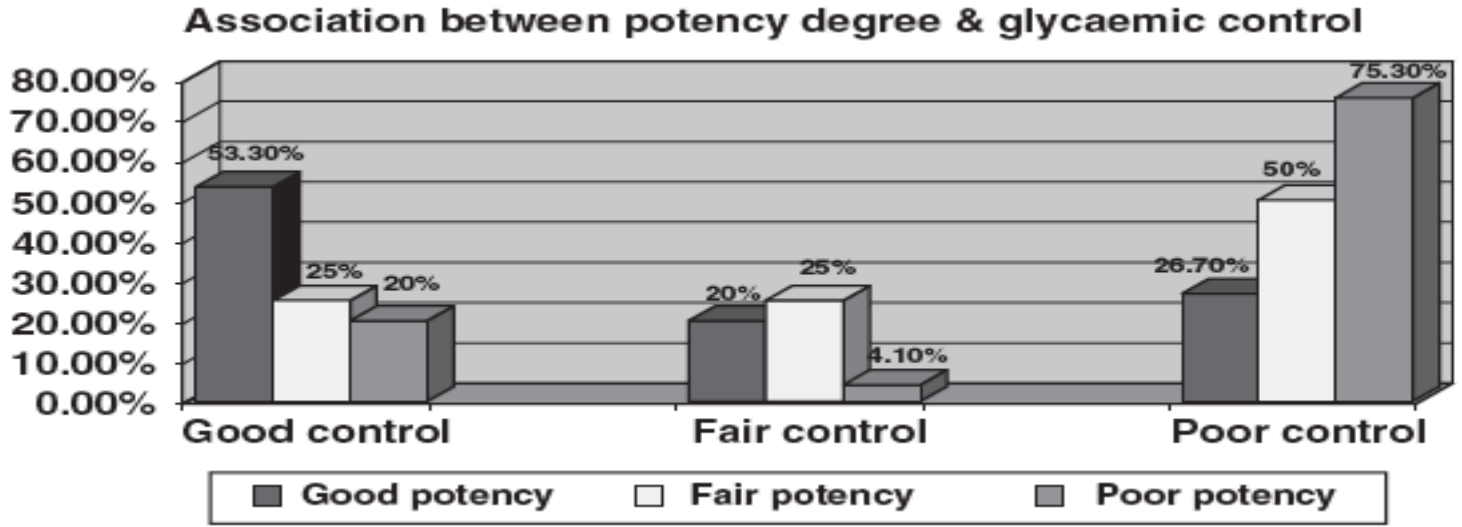



**Figure 1** Response rate of sildenafil according to the complication. MS = patients with metabolic syndrome; DM = patients with diabetes mellitus; HT = patients with hypertension; HL = patients with hyperlipidemia; PLV = patients with history of pelvic surgery.

**Suetomi T et al. J Sex Med 2008**

# PDE5is – management of nonresponders

**Improvement of related comorbid conditions**




**Optimal diabetes control** mirrored by gycosylated hemoglobin **may improve responsiveness to PDE5** inhibitor therapy

**Awad H et al. Int J impot Res 2010**

# Ejaculation disorders

# Ejaculation Disorders & Diabetes

**Retrograde ejaculation**

- *Organic causes*
  - Spinal cord injury
  - Diabetic neuropathy
  - Multiple sclerosis
  - Myelodysplasia
  - Cerebrovascular accidents
  - Congenital (posterior urethral valves, utricular cysts, and extrophy)
- *Iatrogenic causes*
  - Lumbar sympathectomy
  - Retroperitoneal lymph node dissection
  - Aortoiliac vascular surgery
  - Abdominoperineal resection
  - Transurethral bladder neck incision and transurethral resection of prostate
  - Drugs (psychotropic drugs)

Apart from iatrogenic causes, **diabetes mellitus** is the main aetiological factor causing retrograde ejaculation. **The frequency of this disorder in patients with diabetes (both types 1 and 2) ranges from 6% to 40%**

**Anejaculation**

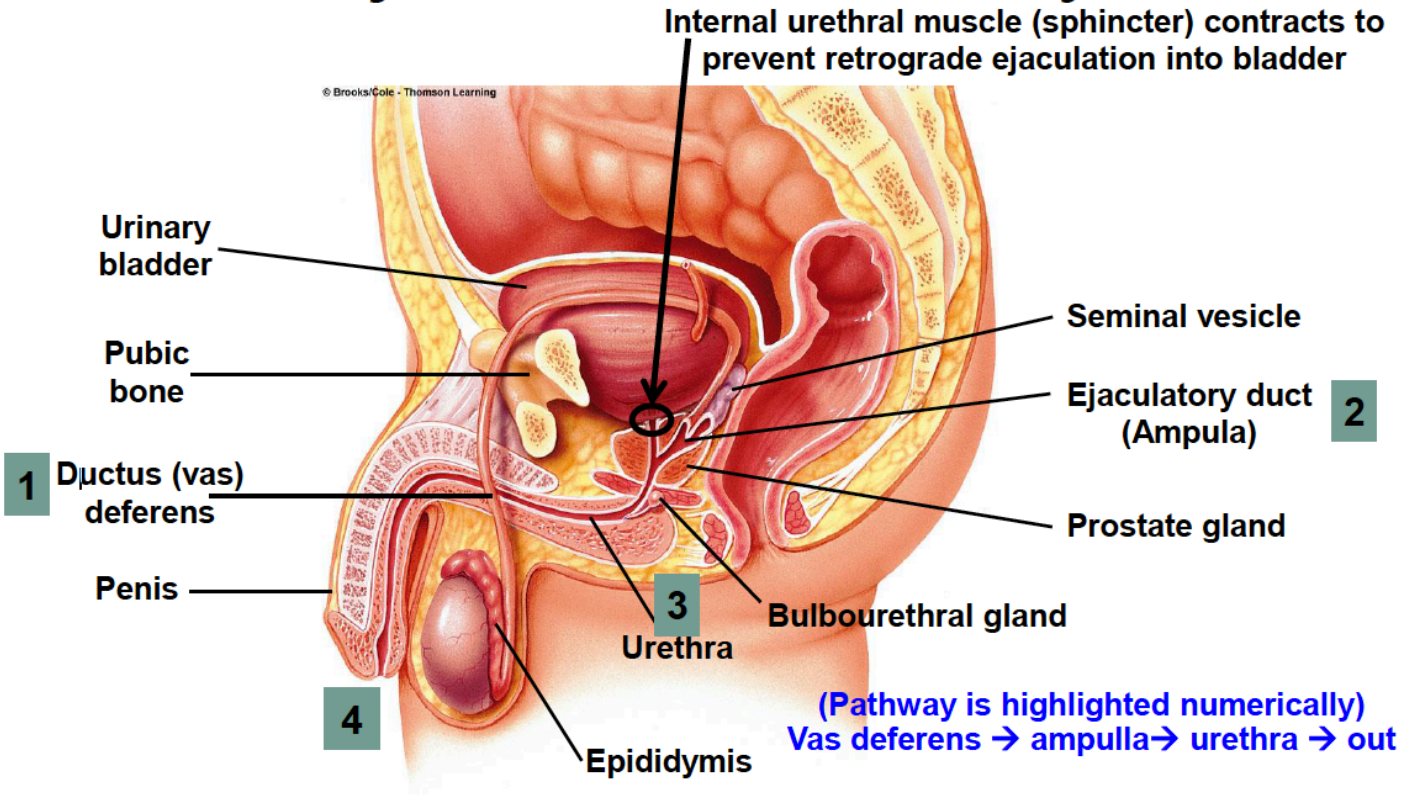
- *Organic causes*
  - Spinal cord injury
  - Diabetic neuropathy
  - Multiple sclerosis
  - Transverse myelitis
  - Vascular spine injuries
  - Congenital spinal anomalies (such as spina bifida)
  - Hormonal disorders (hyperprolactinaemia, hypogonadism, and hypothyroidism)
- *Iatrogenic causes*
  - Retroperitoneal lymph node dissection
  - Prostatectomy
  - Rectal surgery
  - Pelvic radiation
  - Drugs (psychotropic drugs and α-blockers)
- *Relational causes*
- *Psychogenic causes*
  - Fear
  - Anxiety
  - Hostility
  - Relationship difficulties
  - Orthodoxy of religious belief
  - Autosexual orientation
  - Disparity between sex reality and the use of sexual fantasy

Diabetes may be also a rare cause of anejaculation (<10% of all causes)

**Lotti F et al. Nature Reviews Urology 2018**

Sherwood, L., Human Physiology, Fig. 20-1a, p. 733

# Ejaculation Pathway




In some instances (multiple sclerosis, diabetes, after some prostate surgeries), a male may experience retrograde ejaculations due to destruction of his sphincter vesiculi.

# Ejaculation Disorders & Diabetes

**Table 6: Aetiology of anejaculation and retrograde ejaculation [256]**

| Neurogenic | Pharmacological |
|---|---|
| Spinal cord injury | Antihypertensives, Thiazide diruetics |
| Cauda equina lesions | α1-adrenoceptor antagonists |
| Multiple sclerosis | Antipsychotics and antidepressants |
| Autonomic neuropathy (diabetes mellitus) | Alcohol |
| Retroperitoneal lymphadenectomy | Antiandrogens |
| Sympathectomy or aortoiliac surgery | Ganglion blockers |
| Prostate, colorectal and anal surgery | **Endocrine** |
| Parkinson´s disease | Hypothyroidism |
| Diabetes mellitus | Hypogonadism |
| Psychological/behavourial | Hyperprolactinaemia |
| **Urethral** | **Bladder neck incompetence** |
| Ectopic ureterocele | Congenital defects/dysfunction of hemitrigone |
| Urethral stricture | Bladder neck resection (transurethral resection of the prostate) |
| Urethral valves or verumontaneum hyperplasia | Prostatectomy |
| Congenital dopamine β-hydroxylase deficiency | |

**Diabetic neuropathy developing usually because of diabetes mellitus type 1 (DM1)** is responsible for retrograde ejaculation (RE) in **5–18% of cases**

# Ejaculation Disorders & Diabetes

**Table 7: Drug therapy for retrograde ejaculation**

| Drug | Dosage regimen | Ref. |
|---|---|---|
| **Retrograde ejaculation** | | |
| Ephedrine sulphate | 10-15 mg four times daily | [261] |
| Pseudoephedrine | 60 mg four times daily | [262] |
| Midodrine | 7.5–15 mg daily | [262] |
| Imipramine | 25 mg twice daily | [262] |
| Brompheniramine maleate | 8 mg twice daily | [263] |
| Desipramine | 50 mg every second day | [264] |
| **Delayed ejaculation** | | |
| Midodrine | 5–40 mg daily | [256] |
| Imipramine | 25-75 mg daily | |
| Pseudoephedrine | 60 mg – 1200 mg daily | |
| Yohimbine | 20-45 mg prior | |
| Cyproheptadine | 4-12 mg prior | |
| Amantadine | 100-400 mg daily | |
| Cabergoline | 0.5 mg twice a week | |

Sperm collection from post-orgasmic urine for use in ART is recommended if:

- drug treatment is ineffective or intolerable as a result of side-effects;
- the patient has a spinal cord injury;
- drug therapy inducing retrograde ejaculation cannot be interrupted.

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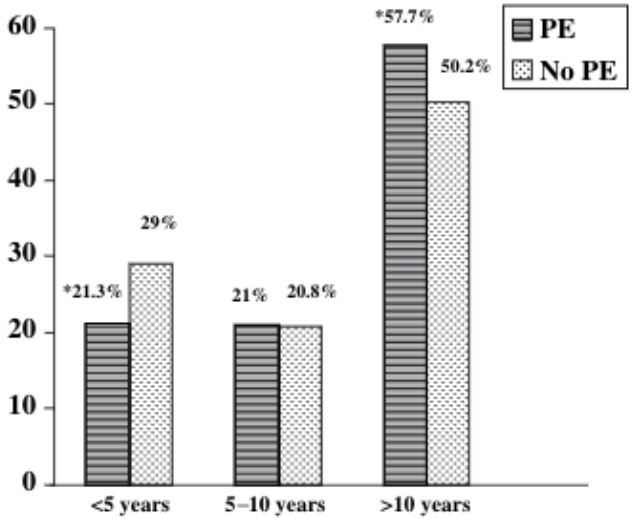
# Ejaculation Disorders & Diabetes

## Premature ejaculation in non-insulin-dependent diabetic patients




**The prevalence of PE was 32.4% in patients below 50 years,which increased to 67.6% in patients above 50 years.**

El Sakka Int J Androl 2003 Dec;26(6):329-34

# Low sexual desire
# (late onset hypogonadism)

# Late Onset Hypogonadism

defects in virilisation and ambiguous genitalia (micropenis, hypospadias, cryptorchidism) [5, 34]. Delay in puberty with an overall eunochoidal phenotype (scant body hair, high-pitched voice, small testis, penis and prostate) is typical of defects manifesting in the pre- or peri-pubertal period due to milder central (isolated HH) or peripheral defects (such as in Klinefelter syndrome) [5, 34]. When hypogonadism occurs in adulthood, especially in the case of functional hypogonadism, symptoms can be often relatively mild, difficult to recognise and frequently confused with the aging process [5, 34] or with the comorbid chronic conditions. Several non-specific clinical features such as fatigue, weakness, and decreased energy, as well as sexual impairment may be clinical manifestations. The EMAS study showed that a triad of sexual symptoms, including low libido, reduced spontaneous erections and ED, are typically associated with a decrease in testosterone serum levels [10]. Conversely, psychological and physical symptoms were less informative [10].

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# Late Onset Hypogonadism

| | Sexual symptoms | Physical symptoms | Psychological symptoms |
|---|---|---|---|
| **More specific** | - Reduced libido<br>- Erectile dysfunction<br>- Decreased spontaneous/ morning erections | - Decreased vigorous activity<br>- Difficulty walking >1 km<br>- Decreased bending | - Low mood/mood deflection<br>- Decreased motivation<br>- Fatigue |
| **Less specific** | - Reduced frequency of sexual intercourse<br>- Reduced frequency of masturbation<br>- Delayed ejaculation | - Hot flushes<br>- Decreased energy<br>- Decreased physical strength/function/activity | - Concentration or mnemonic difficulties<br>- Sleep disturbances |

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# Late Onset Hypogonadism

**AGE**  **Obesity**  **Comorbidities**

**DMT2**

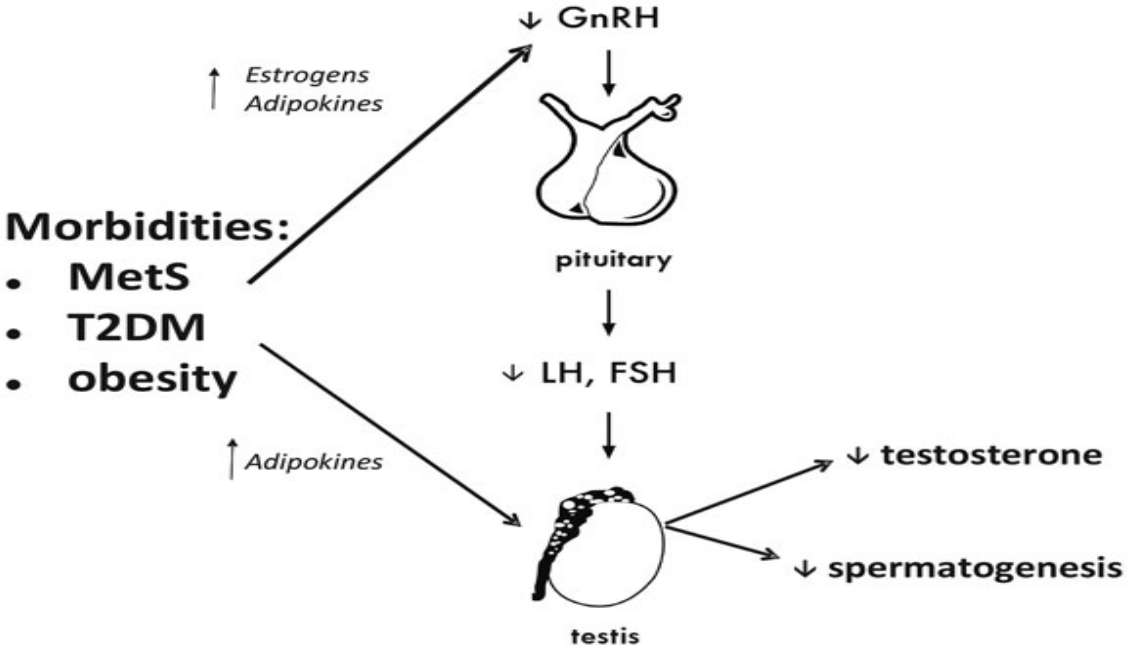
Metabolic syndrome

COPD

Renal disease

# Late Onset Hypogonadism

***Hormonal Dysregulation***




Corona et al. Hormones 2015; 14(4):569-578

# Late Onset Hypogonadism

## *Hormonal Dysregulation*

- At least 25% of men with **type II DM** have:
  **subnormal free T concentrations**
  inappropriately **low LH and FSH** concentrations

Dandona P, et al. J Clin Endocrinol Metab, 96:2643-51, 2011

| | |
|---|---|
| hypogonadotropic hypogonadism | 25–40% |

Kapoor D, et al. Diabetes Care , 30:911–7, 2007
Rhoden EL, et al. BJU Int, 96:867–70, 2005
Grossmann M, et al. J Clin Endocrinol Metab , 93:1834–40, 2008
Corona G, et al. Int J Impot Res, 18:190–7, 2006

- Another 4% of men with **type II DM** have:
  **subnormal total T concentrations**
  **elevated LH and FSH** concentrations

| | |
|---|---|
| hypergonadotropic hypogonadism | 4% |

Dandona P, et al. J Clin Endocrinol Metab, 96:2643-51, 2011

# Male Infertility

# Infertility & Diabetes – What is the link?

## Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts

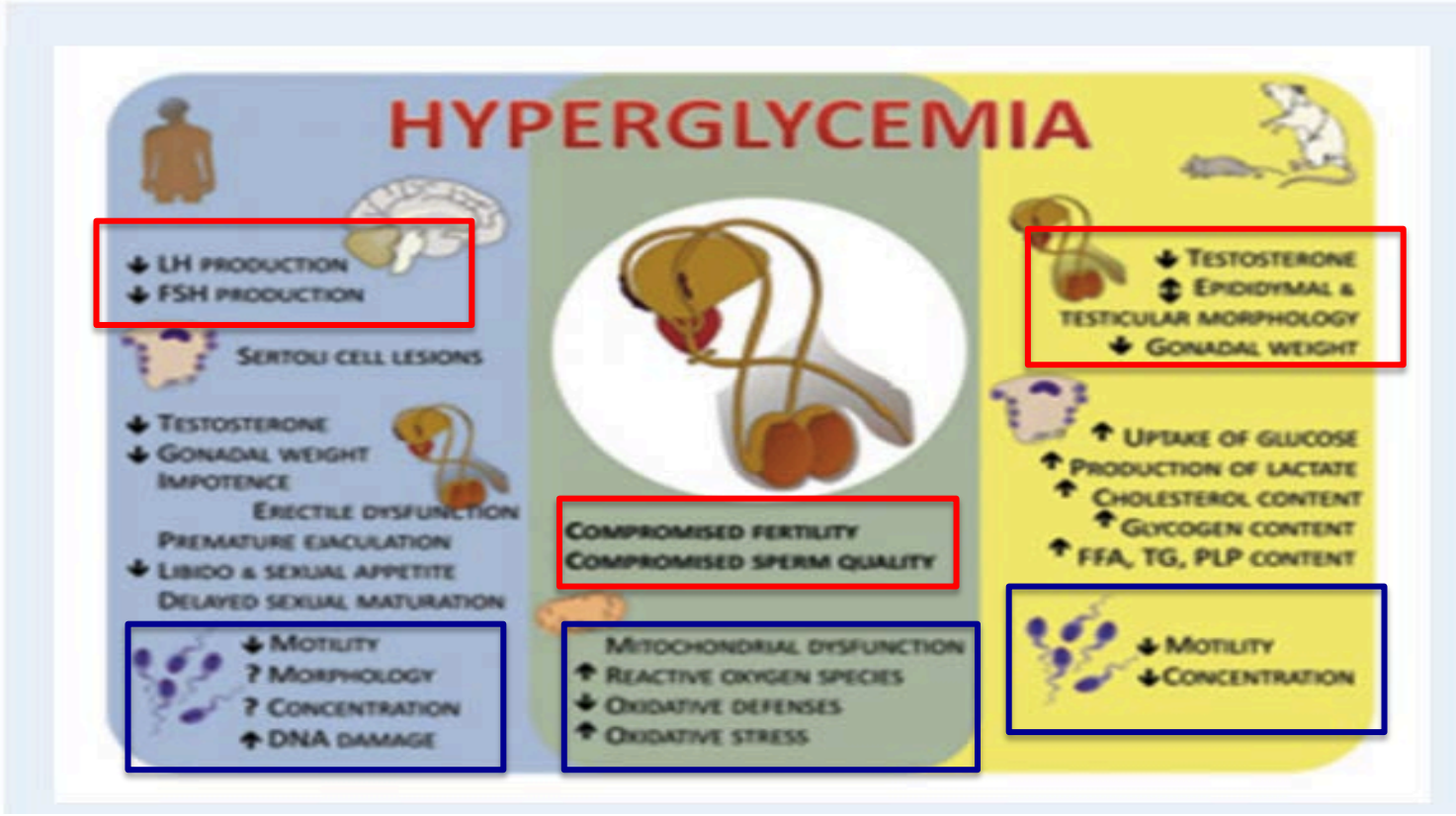
Disorders of ejaculation are uncommon, but important causes of male infertility

**Table II** *Continued*

| Causal factors for severe male infertility | Full group n = 1737 | | Aspermia n = 46 | |
|---|---|---|---|---|
| | n | % | n | % |
| *5.1. Anorgamia (in case of vaginal sex)* | 8 | 0.5 | 4 | 8.7 |
| Spinal trauma | 3 | 0.2 | 3 | 6.5 |
| Diabetes mellitus | 1 | 0.1 | 1 | 2.2 |
| Masturbation successful, idiopathic | 3 | 0.2 | | |
| Masturbation successful, spinal trauma | 1 | 0.1 | | |
| *5.2. Anejaculation* | 20 | 1.2 | 20 | 43.5 |
| Spinal trauma | 13 | 0.7 | 13 | 28.3 |
| Diabetes mellitus | 2 | 0.1 | 2 | 4.3 |
| Sclerosis multiplex | 1 | 0.1 | 1 | 2.2 |
| Epilepsy | 1 | 0.1 | 1 | 2.2 |
| Idiopathic | 3 | 0.2 | 3 | 6.5 |
| *5.3. Retrograde ejaculation (total)* | 9 | 0.5 | 9 | 19.6 |
| Diabetes mellitus | 6 | 0.3 | 6 | 13 |
| Post TURP | 1 | 0.1 | 1 | 2.2 |
| Idiopathic | 2 | 0.1 | 2 | 4.3 |
| *5.4. Retrograde ejaculation (partial)* | 39 | 2.2 | | |
| Diabetes mellitus | 5 | 0.3 | | |
| Spinal trauma | 4 | 0.2 | | |
| Hypospadia operations | 1 | 0.1 | | |
| Post TURP | 1 | 0.1 | | |
| Serious pelvic trauma | 1 | 0.1 | | |

Punab et al. Human Rep 2017; 32: 18–31

# Infertility & Diabetes – What is the link?



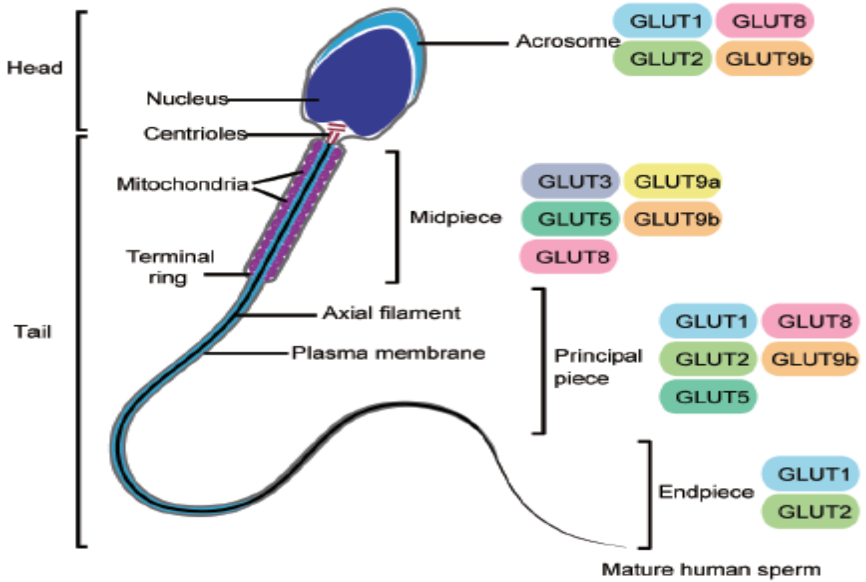

Maresch et al. Human Rep Upd 2018; 24:86–105

# Infertility & Diabetes – What is the link?

Sperm mainly utilize **sugars as an energy fuel** including glucose, mannose, and fructose

Glucose passively transport across the blood-testis barrier, which is mediated by **GLUTs**, is an important event in spermatogenesis.

GLUTs also exist in mature sperm cells, which, in fact, require carriers for uptake energetic sources that are im**portant for maintaining basic cell activity, as well as specific functions**, such as motility and fertilization ability.




However, an **abnormal environment like diabetes can cause the dysfunction in nutrient transport**, thus leading to the decreased fertility and adverse fetal outcomes

Ding et al. AJA 2015; 17, 948–953

# Infertility & Diabetes – What is the link?

**Table 1: The detrimental effects of male diabetes on sperm quality**

| *Detrimental effects* | *References* |
|---|---|
| Impairment of spermatogenesis, reduced sperm count and motility | 8,39,48,51,52,57,59–61 |
| Male subfertility (decreased fertility potential) by altering steroidogenesis and sperm motility | 37,51–57 |
| Testicular and erectile dysfunctions | 8,39,52 |
| Impairment of sperm DNA integrity | 8,40,43,44,48,59 |
| Effect on ingredients of seminal plasma | 49,50 |
| Epigenetic dysregulation during spermatogenesis | 78,79 |

Ding et al. AJA 2015; 17, 948–953

# Infertility & Diabetes – What is the link?

***Oxidative stress***

Numerous factors have been shown to increase oxidative stress (OS), ROS production, and **sperm DNA damage**

**Advanced glycation end products (AGE)**, resulting from the binding of sugars to proteins, lipids, and nucleic acids, have been implicated as **key pathogenic factors in many diabetic complications diabetes**

**Hyperglycemia → ↑ AGE →**

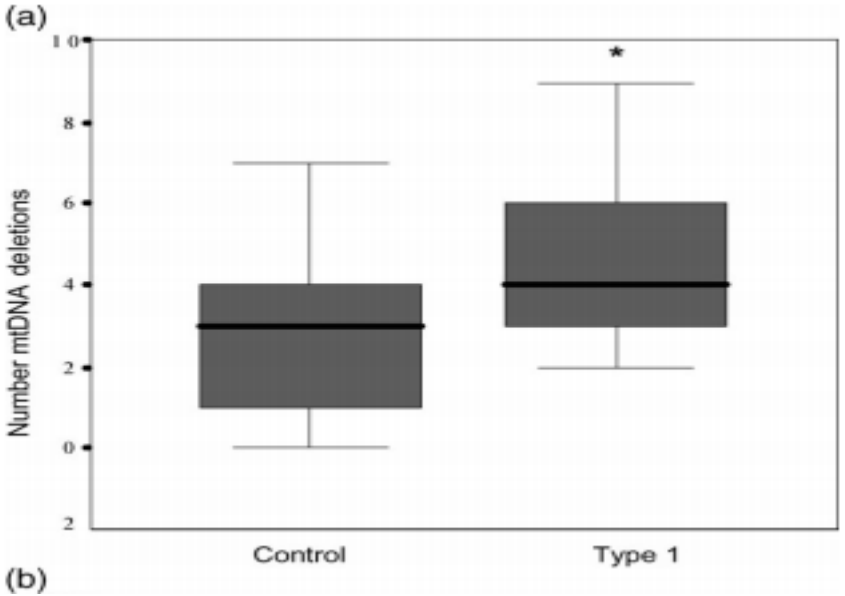
1. **Direct damage to macromolecules**

1. **Interactions with RAGE →**
   ↑ molecules implicated in inflammatory responses and tissue damage:
   - **cytokines**
   - **adhesion molecules**
   - **Matrix metalloproteinases**

Pergialiotis et al. J Diabetes Complications. 2016;30:1167-76
Ding et al. Asian J Androl 2015; 17, 948–953
La Vignera et al. J Androl 2012; 2: 145 - 153

# Infertility & Diabetes – What is the link?

**Men with DM had increased spermatozoa nuclear and mitochondrial DNA damages than controls**, thus leading to impaired reproductive capability




Agbaje et al, Hum Reprod 2007; Hum Reprod 2007; 22:1871–7

# Are diabetic patients at higher risk of infertility?

**Association between abnormal semen parameters and diseases stratified by organ system.**

| Disease category | No. of patients | Semen abnormalities (volume, concentration, motility) 0 | 1 | 2+ | *P* value |
|---|---|---|---|---|---|
| Infections and parasitic diseases | | | | | |
| No | 8,905 | 4,665 (55.8) | 2,580 (30.8) | 1,121 (13.4) | .27 |
| Yes | 55 | 27 (52.9) | 13 (25.5) | 11 (21.6) | |
| Endocrine disease, nutritional, metabolic disorders | | | | | |
| No | 8,612 | 4,534 (55.9) | 2,496 (30.8) | 1,076 (13.3) | .02 |
| Yes | 348 | 158 (50.8) | 97 (31.2) | 56 (18.0) | |

Eisenberg et al. 2015 Fertil Steril;103

**Table 3 – Diagnostic categories, International Classification of Diseases modified ninth version (ICD-9-CM) codes, and Charlson Comorbidity Index (CCI) weights in infertile and fertile men with CCI ≥1**

| Condition | ICD-9-CM codes | CCI weights | Infertile men, *n* (%) | Fertile men, *n* (%) |
|---|---|---|---|---|
| Diabetes | | | | |
| Diabetes mellitus | 250 | 1 | 11 (3.2) | 3 (1.0) |

Salonia et al. Eur Urol 2009; 56; 1025 – 1032

The number of patients with metabolic alterations was found to be significantly higher among patients with semen alterations

# *Are diabetic patients at higher risk of infertility?*

Diabetes mellitus has been associated with male infertility in several reports

| | Study design | Patients | Main outcome | Main findings |
|---|---|---|---|---|
| Agbaje et al [42] | Case - Control | 27 patients with DM vs. 29 controls | Semen quality and DM | Significantly lower semen quality and DNA fragmentation among patients with DM |
| Bener et al [44] | Retrospective cohort | 857 married men | Infertility and DM | The prevalence of MI was significantly higher among patients with DM |
| La Vignera et al [45] | Case - Control | 32 patients with type 1 DM vs. 20 controls | Semen quality and DM | Patients with type 1 DM had lower sperm concentration and sperm motility |
| Pergialiotis et al [46] | Meta-analysis | 1,855 patients from 13 studies | Seminal quality and DM | 14.29% decrease of percentage of motile cells among patients with DM compared to controls |

Capogrosso P et al. Minerva Urol Nephrol 2018

# *Are diabetic patients at higher risk of infertility?*

Hyperglycemia was associated with a reduced number of offspring

**Table 1** Basic characteristics, mean number of children and frequency of childlessness in 697 individuals with Type 1 diabetes mellitus

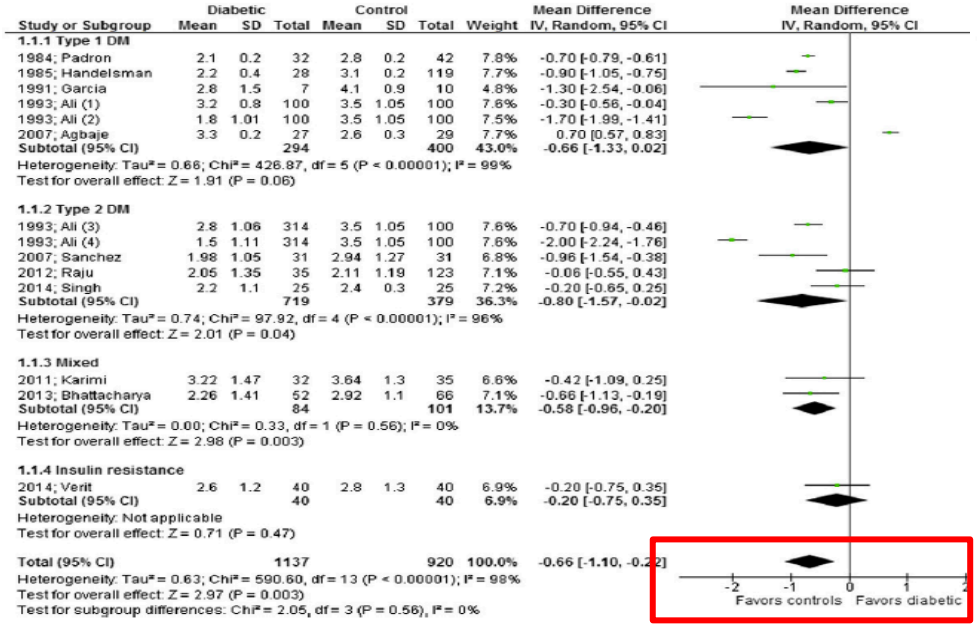
| Variable | Women with Type 1 diabetes ($n$ = 364) | Men with Type 1 diabetes ($n$ = 333) |
|---|---|---|
| Age at survey 2010 (years) | 46.6 ± 16.9 | 45.9 ± 16.4 |
| Duration of diabetes (years) | 23.2 ± 15.1 | 21.6 ± 14.9 |
| Age by manifestation of diabetes (years) | 23.6 ± 15.2 | 24.2 ± 13.0 |
| Mean total number of children | 1.10 ± 1.02 | 0.99 ± 1.29 |
| Mean number of children born after manifestation of diabetes | 0.62 ± 0.87 | 0.57 ± 1.05 |
| Frequency of childlessness | 35.7% (130/364) | 51.1% (170/333) |
| Frequency of childlessness in the age group of 41–45 years | 36.2% (17/47) | 52% (26/50) |

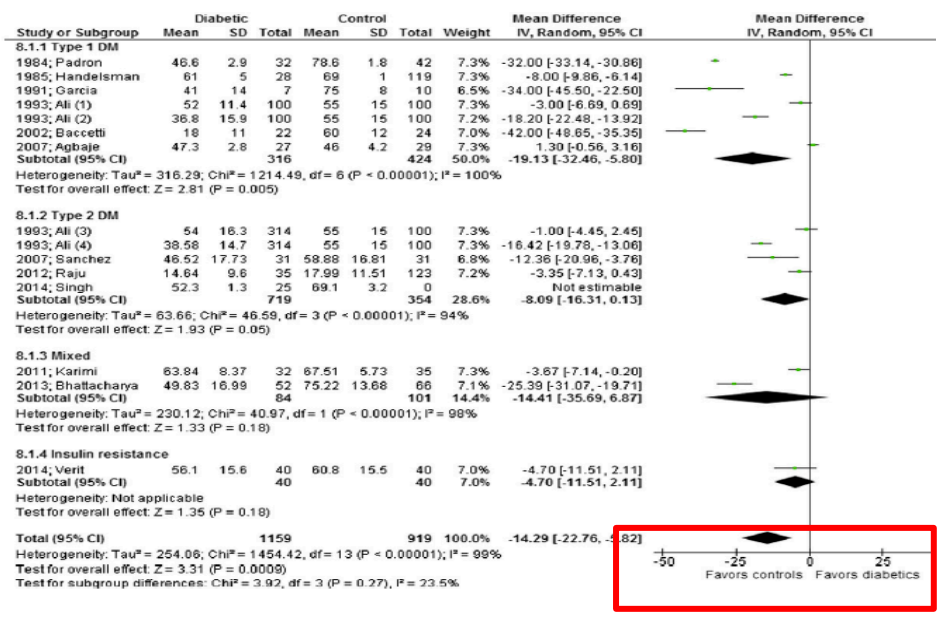
Compared with 1.36 children per subject in the German background population, the total fertility rate in the calendar year of 2010 in the cohort with **Type 1 diabetes (age 18-49 years) was 0.88.**

Holstein et al. Diabet. Med. 2012;29: 1268–1271

# *Are diabetic patients at higher risk of infertility?*

Meta-analysis including 12 observational studies

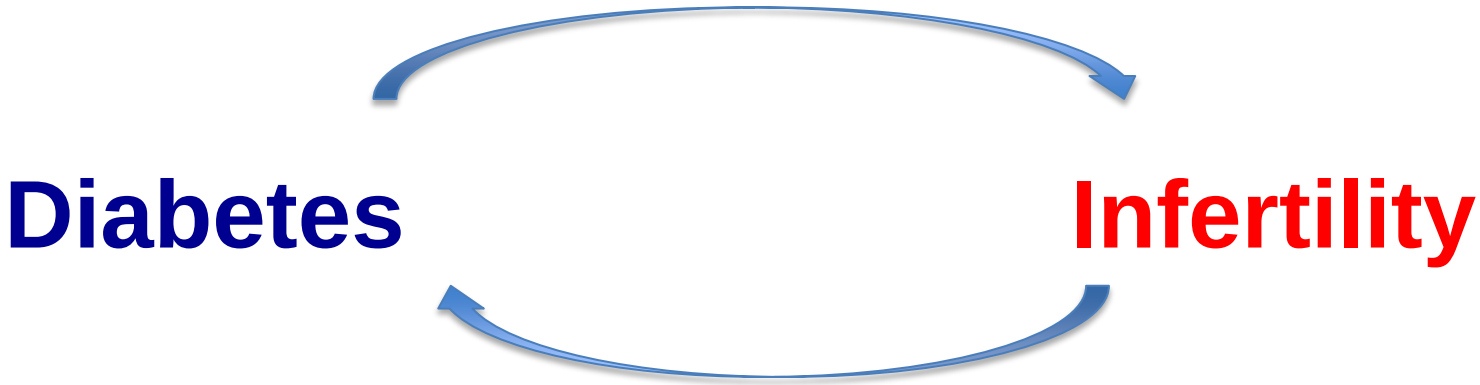



**DM decreases the seminal volume and the percentage of motile cells**

14.29% decrease of percentage of motile cells among patients with DM compared to healthy controls

Pergialiotis et al. J Diabetes Complications. 2016;30:1167-76


Diabetes
Infertility

# *Are infertile men at higher risk of diabetes?*

## Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data

Michael L. Eisenberg, M.D.,[a] Shufeng Li, M.S.,[b] Mark R. Cullen, M.D.,[c] and Laurence C. Baker, Ph.D.[d]

**Number of men and incidence of medical comorbidity diagnosis for each subdiagnosis of male infertility compared with infertility testing alone.**

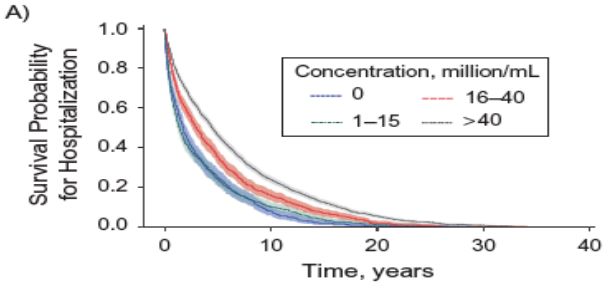
| | | Azoospermia (606.0) | | Oligospermia (606.1) | | Infertility, extratesticular causes (606.8) | | Male infertility, unspecified (606.9) | |
|---|---|---|---|---|---|---|---|---|---|
| **Disease** | **Infertility testing** | **n (%)** | **HR (95% CI)** | **n (%)** | **HR (95% CI)** | **n (%)** | **HR (95% CI)** | **n (%)** | **HR (95% CI)** |
| Hypertension | 1,413 (5.92) | 146 (7.50) | 1.00 (0.84–1.19) | 318 (7.43) | 1.06 (0.94–1.20) | 75 (7.20) | 0.89 (0.70–1.12) | 435 (6.93) | 1.07 (0.96–1.19) |
| Diabetes | 310 (1.30) | 43 (2.21) | 1.34 (0.97–0.84) | 88 (2.06) | 1.33 (1.05–1.68)[a] | 28 (2.69) | 1.50 (1.00–2.23)[a] | 105 (1.67) | 1.20 (0.96–1.50) |
| Hyperlipidemia | 1,746 (7.32) | 160 (8.22) | 0.89 (0.75–1.04) | 373 (8.71) | 1.03 (0.92–1.15) | 103 (9.88) | 1.05 (0.85–1.28) | 526 (8.37) | 1.04 (0.95–1.15) |
| Renal disease | 51 (0.21) | 12 (0.62) | 2.26 (1.20–4.27)[a] | 14 (0.33) | 1.29 (0.71–2.33) | 6 (0.58) | 2.03 (0.84–4.91) | 21 (0.33) | 1.39 (0.83–2.33) |
| Chronic pulmonary disease | 908 (3.81) | 91 (4.67) | 0.97 (0.78–1.20) | 171 (3.99) | 0.90 (0.76–1.06) | 54 (5.18) | 0.99 (0.75–1.32) | 258 (4.11) | 1.00 (0.87–1.15) |
| Liver disease | 280 (1.17) | 20 (1.03) | 0.68 (0.43–1.07) | 73 (1.70) | 1.28 (0.99–1.65) | 26 (2.50) | 1.60 (1.06–2.43)[a] | 81 (1.29) | 1.02 (0.80–1.31) |
| Depression | 506 (2.12) | 74 (3.80) | 1.45 (1.13–1.85)[a] | 112 (2.62) | 1.07 (0.87–1.32) | 38 (3.65) | 1.30 (0.93–1.83) | 173 (2.75) | 1.20 (1.01–1.43)[a] |
| Peripheral vascular disorders | 71 (0.30) | 8 (0.41) | 1.01 (0.48–2.12) | 16 (0.37) | 1.07 (0.62–1.85) | 4 (0.38) | 1.00 (0.37–2.76) | 24 (0.38) | 1.19 (0.74–1.91) |
| Cerebrovascular disease | 97 (0.41) | 17 (0.87) | 1.62 (0.96–2.73) | 22 (0.51) | 1.07 (0.671.71) | 5 (0.48) | 0.88 (0.36–2.18) | 30 (0.48) | 1.04 (0.69–1.58) |
| Ischemic heart disease | 171 (0.72) | 26 (1.34) | 1.35 (0.89–2.06) | 50 (1.17) | 1.35 (0.98–1.85) | 18 (1.73) | 1.60 (0.96–2.65) | 79 (1.26) | 1.56 (1.19–2.05)[a] |
| Other heart disease | 533 (2.23) | 55 (2.82) | 0.96 (0.73–1.27) | 147 (3.43) | 1.32 (1.10–1.59)[a] | 26 (2.50) | 0.77 (0.51–1.16) | 180 (2.87) | 1.17 (0.99–1.39) |
| Injury | 4,400 (18.44) | 439 (22.55) | 1.04 (0.94–1.15) | 904 (21.11) | 1.00 (0.93–1.08) | 222 (21.31) | 0.96 (0.84–1.10) | 1,360 (21.65) | 1.10 (1.03–1.17)[a] |
| Alcohol abuse | 76 (0.32) | 15 (0.77) | 1.94 (1.11–3.39)[a] | 25 (0.58) | 1.60 (1.02–2.52)[a] | 7 (0.67) | 1.63 (0.74–3.58) | 31 (0.49) | 1.36 (0.89–2.07) |
| Drug abuse | 36 (0.15) | 5 (0.26) | 1.16 (0.44–3.04) | 8 (0.19) | 1.08 (0.50–2.33) | 5 (0.48) | 2.32 (0.87–6.21) | 21 (0.33) | 2.03 (1.17–3.52)[a] |
| Anxiety disorders | 504 (2.11) | 57 (2.93) | 1.11 (0.84–1.46) | 109 (2.55) | 1.07 (0.87–1.31) | 31 (2.98) | 1.08 (0.74–1.56) | 165 (2.63) | 1.17 (0.98–1.40) |
| Bipolar disorders | 46 (0.19) | 7 (0.36) | 1.43 (0.64–3.19) | 5 (0.12) | 0.54 (0.21–1.35) | 1 (0.10) | 0.29 (0.04–2.43) | 15 (0.24) | 1.23 (0.68–2.22) |

men diagnosed with male factor infertility had a higher risk of developing diabetes (HR 1.30, 95% CI 1.10–1.53),

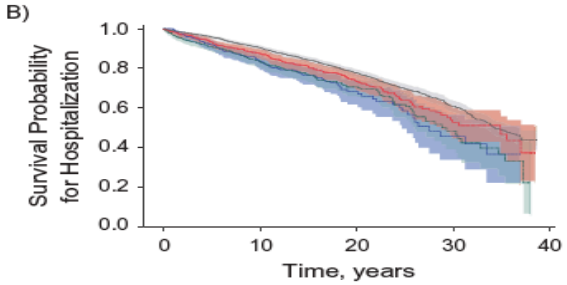
Eisenberg et al. Fertil Steril 2016; 105

# *Are infertile men at higher risk of diabetes?*

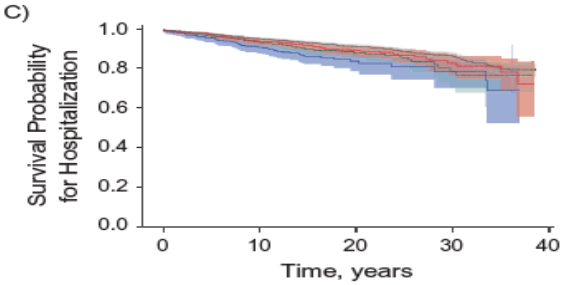
Overall




CVD




**Diabetes**




**Men with low semen quality more often required hospitalization in particular for diabetes mellitus and cardiovascular disease**

Latif et al.-Am J Epidemiol. 2017;186(8):910-917

# *Are infertile men at higher risk of diabetes?*

## Risk of diabetes according to male factor infertility: a register-based cohort study

**Table II** Association between male factor infertility and risk of diabetes.

| | Men at risk, *n* | Cases, *n* | Hazard ratios (95% CI) Crude[a,b] | Hazard ratios (95% CI) Adjusted model[a,b,c] |
|---|---|---|---|---|
| First IVF period (1994–2005) | | | | |
| Reference | 8641 | 286 | 1.00 | 1.00 |
| Male factor infertility | 5642 | 175 | 1.06 (0.87, 1.27) | 1.08 (0.89, 1.31) |
| Second IVF period (2006–2012) | | | | |
| Reference | 12 376 | 61 | 1.00 | 1.00 |
| Male factor infertility | 12 857 | 129 | 1.42 (1.05, 1.93) | 1.45 (1.06, 1.97) |
| Unknown[d] | 10 078 | 74 | 0.99 (0.71, 1.39) | 1.01 (0.715, 1.43) |
| Fertile | 12 376 | 61 | 1.00 | 1.00 |
| Oligospermia[e] | 8538 | 66 | 1.29 (0.91, 1.83) | 1.44 (1.01, 2.063) |
| Other causes/unspecified | 2907 | 38 | 1.31 (0.80, 1.97) | 1.60 (1.04, 2.46) |
| Azoospermia | 1275 | 22 | 2.31 (1.42, 3.77) | 2.10 (1.25, 3.56) |
| Aspermia | 137 | 3 | 3.43 (1.07, 10.94) | 3.20 (1.00, 10.31) |

**The risk of diabetes appeared to increase with the severity of male factor infertility**

The adjusted HR's for diabetes risk among men with male factor infertility when compared to the reference group were **HR = 1.08 (95% CI: 0.89, 1.31) and HR = 1.45 (95% CI: 1.06, 1.97)** for the first and second IVF registration period, respectively

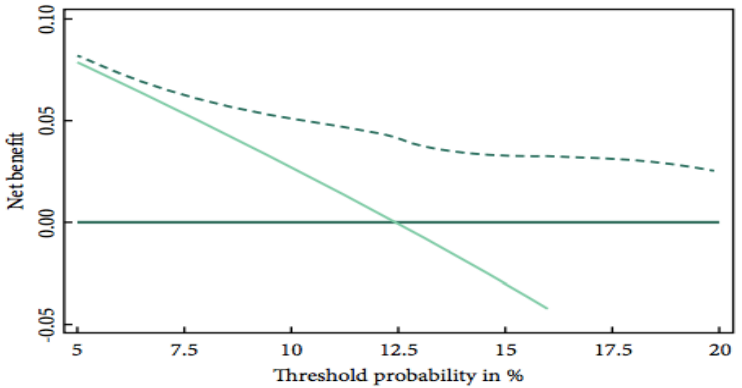
Glazer et al. Human Rep 2017; 32: 1474–81 2017

# Undiagnosed prediabetes is highly prevalent in primary infertile men – results from a cross-sectional study

**One out of ten** men seeking medical help for primary couple's infertility showed glycaemic impairment suggestive for PreDM status

Table 3 Logistic regression models predicting PreDM in the whole cohort.

| | +PreDM | |
|---|---|---|
| | **UVA model OR (95% CI); *P*** | **MVA model OR (95% CI); *P*** |
| Age | 1.08 (1.05–1.12); <0.001 | 1.01 (1.04–1.12); 0.001 |
| BMI | 1.06 (1.01–1.12); 0.045 | 1.08 (0.99–1.16); 0.06 |
| CCI | 1.45 (0.97–2.16); 0.06 | 1.13 (0.64–1.93); 0.70 |
| FSH | 1.04 (1.02–1.06); <0.001 | 1.03 (1.01–1.05); 0.028 |
| Testicular volume | 0.99 (0.95–1.03); 0.64 | 1.03 (0.98–1.08); 0.20 |
| iNOA | 3.38 (2.14–5.32); <0.001 | 1.91 (1.02–3.56); 0.04 |




**Older age, FSH levels and iNOA** achieved independent predictor status for +PreDM

**AUC: 0.73; 95% CI: 0.65 – 0.80**

**Our model showed a higher net benefit** when it is used to discriminate patients at higher risk of having a +PreDM status that need to undergo a further diagnostic evaluation

As confirmed by our predictive model, **these parameters could be used to better identify those patients who may benefit most from hypoglycaemic preventive measures in the real-life setting.**

**Boeri L , et al. BJU Int. 2018, epub**

# *Diabetic control & Male Fertility*

## Metformin improves semen characteristics of oligo-terato-asthenozoospermic men with metabolic syndrome

45 OAT patients were treated with **metformin** for 6 months.

**TABLE 1**

Semen analysis and hormone and metabolic profiles before and after metformin therapy.

| Analysis | Before | After | *P* value |
|---|---|---|---|
| Hormone profile | | | |
| LH (mIU/mL) | 2.5 ± 1.3 | 3.3 ± 1.2 | <.01 |
| FSH (mIU/mL) | 3.4 ± 1.2 | 3.5 ± 1.1 | NS |
| $E_2$ (pg/mL) | 32 ± 5 | 21 ± 3 | <.01 |
| SHBG (nmol/mL) | 55 ± 5 | 35 ± 3 | <.001 |
| Free testosterone (pg/mL) | 33 ± 11 | 47 ± 13 | <.001 |
| Testosterone (ng/mL) | 2.8 ± 1.2 | 3.7 ± 1.4 | <.02 |
| Metabolic profile | | | |
| BMI (kg/cm$^2$) | 28.0 ± 3.5 | 27.3 ± 3.1 | NS |
| WC (cm) | 107 ± 4 | 105.3 ± 3 | NS |
| Triglycerides (mg/dL) | 175 ± 12 | 173.2 ± 13 | NS |
| HOMA | 2.8 ± 1.2 | 1.6 ± 0.7 | <.0001 |
| Semen parameter | | | |
| Concentration ($10^6$/mL) | 16.2 ± 3.4 | 20 ± 4.2 | <.001 |
| Motility (%) | 39 ± 8 | 51 ± 7 | <.001 |
| Normal morphology (%) (normal) | 25 ± 3 | 30 ± 2 | <.001 |

Morgante et al. Fertil Steril 2011;95:2150–52

# Prediabetes in primary infertile men – results from a cross-sectional study

**One out of ten** men seeking medical help for primary couple's infertility showed glycaemic impairment suggestive for PreDM status.

**PreDM status was associated with a further compromised condition in terms of fertility parameters**, thus pointing out the actual importance of glucose metabolism investigation throughout the workup for infertile man.

**Older age, higher FSH values and iNOA** status emerged as independent predictors for +PreDM status in primary infertile men.

As confirmed by our predictive model, **these parameters could be used to better identify those patients who may benefit most from hypoglycaemic preventive measures in the real-life setting.**

Boeri et al. EAU 2018

# Take home message

- **Patients with DM are at higher risk of**
  - Erectile dysfunction
  - Ejaculation disorders
  - Low sexual desire (hypogonadism)
  - Male infertility

- **Glycemic control is associated with improved sexual and reproductive function**

- **Patients with ED and male infertility are at higher risk of unrecognized diabetes**