LA DE: RUOLO DEI NUOVI FARMACI IPOGLICEMIZZANTI

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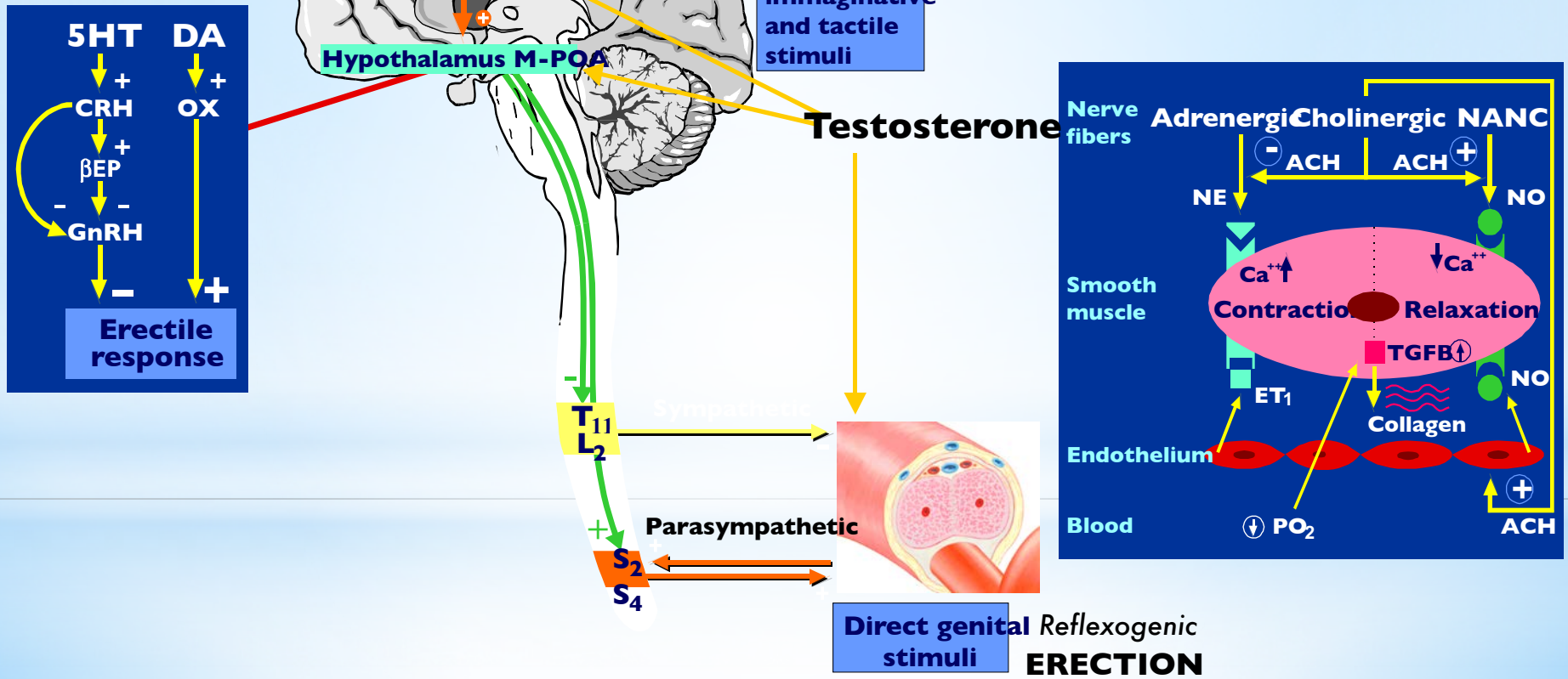
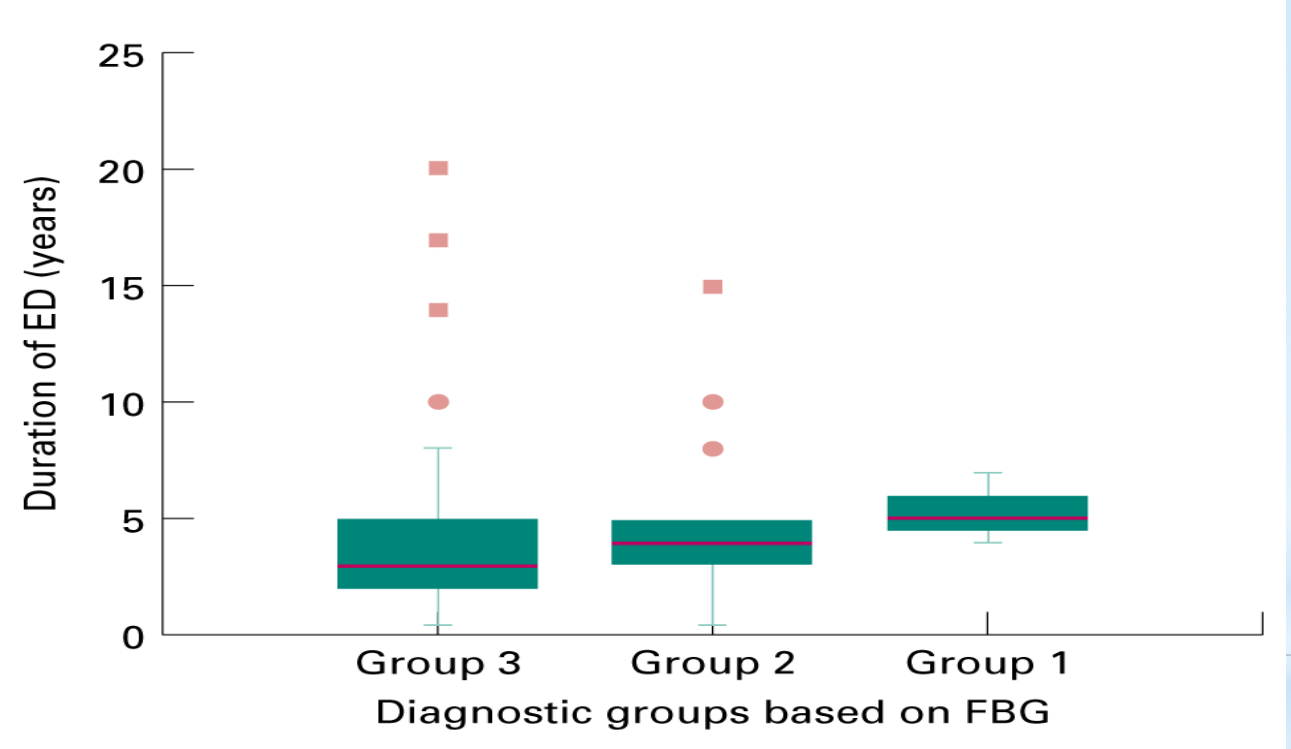
Pol.EUR –ACISMOM
Ambulatorio di Andrologia
Ospedale S.Giovanni Battista
Roma

FISIOLOGIA EREZIONE



J Sex Med 2013;10:130–171

Diabete e deficit erettile: spesso sintomo di esordio



normoglicemia

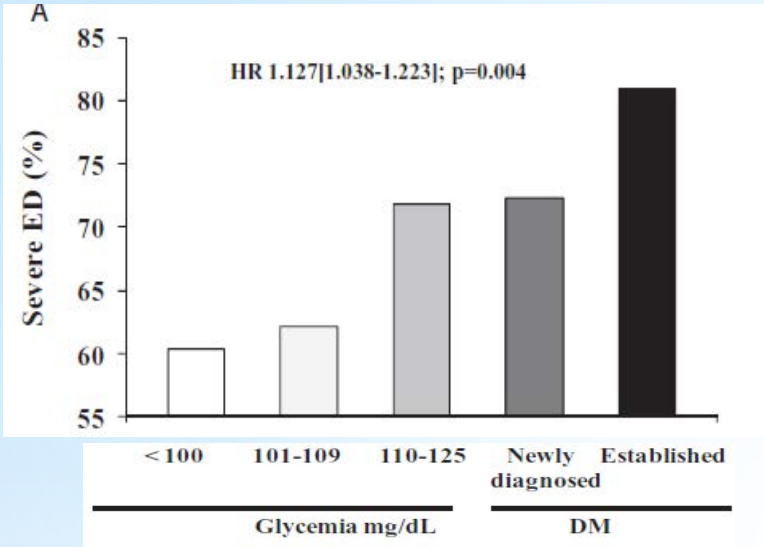
Alterata glicemia A digiuno

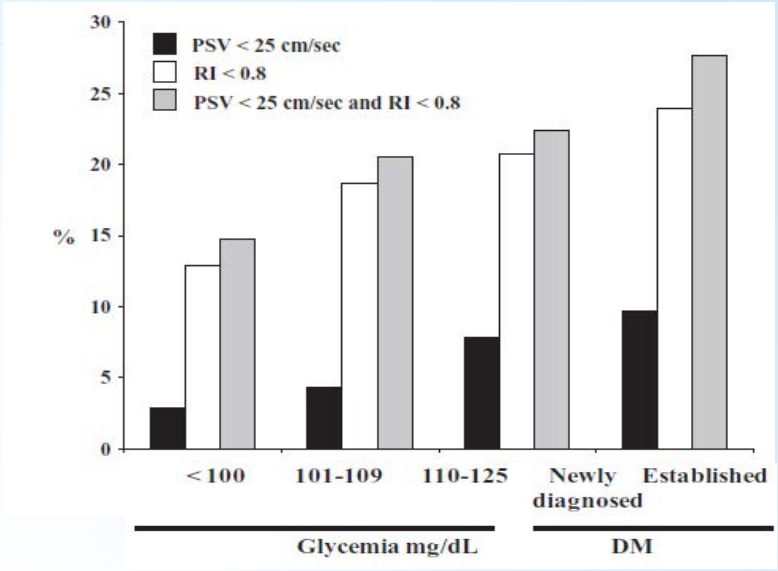
diabetici

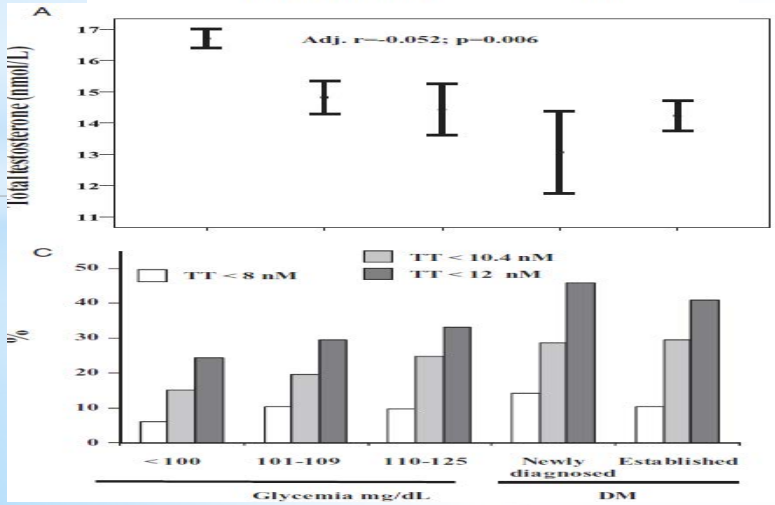
K. Sairam et al., BJU International 2001

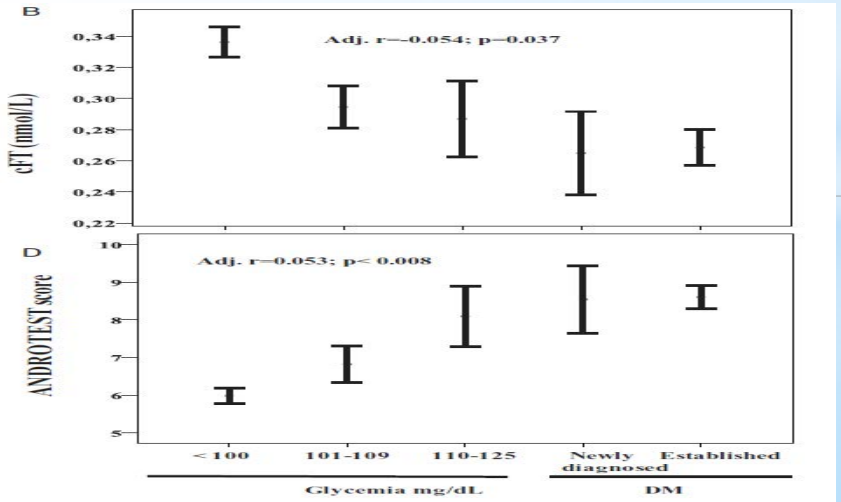
Hormonal Association and Sexual Dysfunction in Patients with Impaired Fasting Glucose: A Cross-Sectional and Longitudinal Study

Giovanni Corona, MD,









J Sex Med 2012;9:1669–1680

Co-morbidity prevalence with low serum T levels in aldult end elderly men

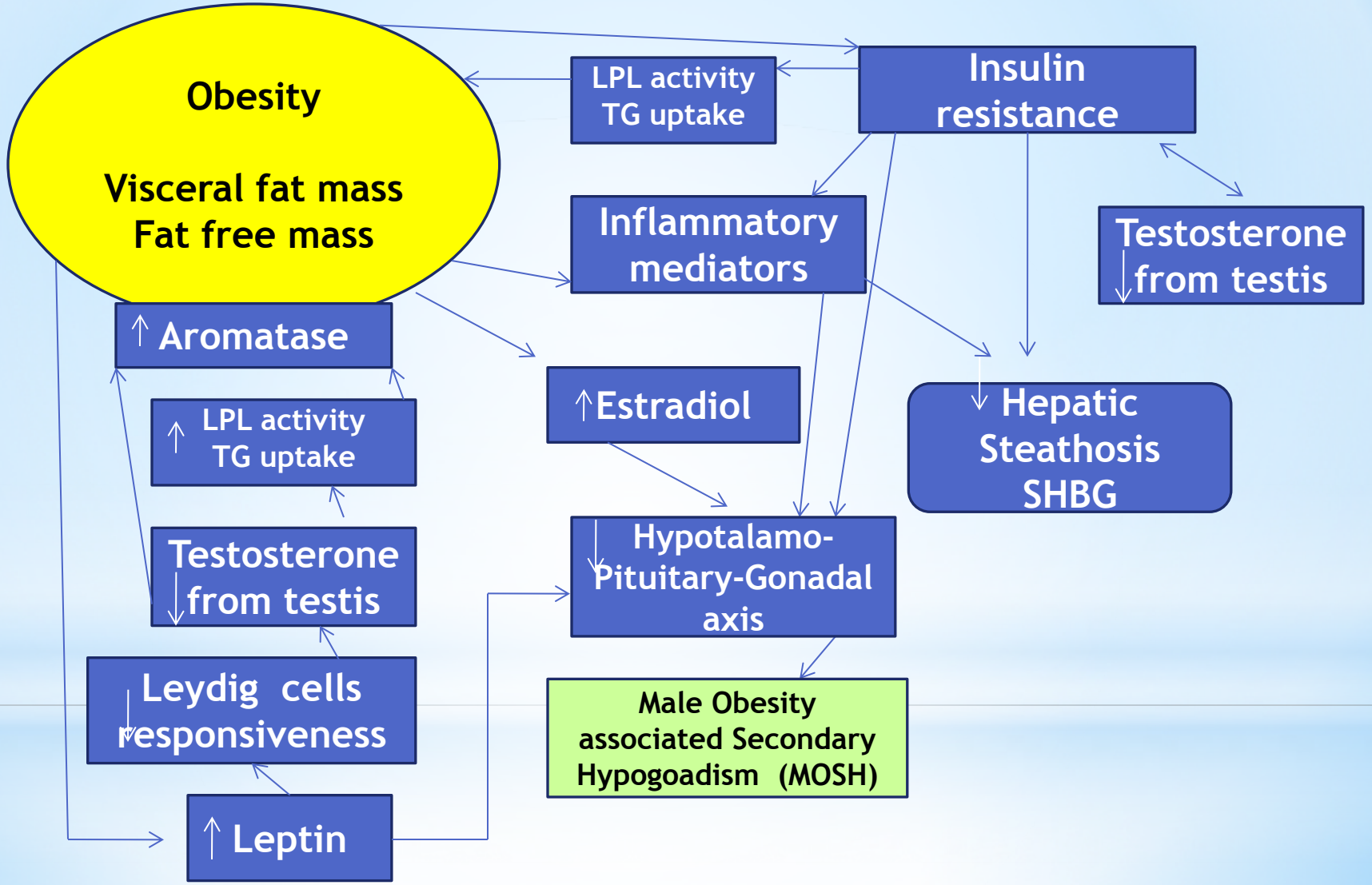
(Mulligan T et al, Int J Clin Prac, 2006)

Condition	*Hypogonadal patients (n = 836)*	*Eugonadal patients (n = 1326)*	*p-value**
Hypertension	547 (65.4)	678 (51.1)	<0.001
Hyperlipidaemia	506 (60.5)	670 (50.5)	<0.001
Diabetes	258 (30.9)	237 (17.9)	<0.001
Obesity	270 (32.3)	225 (17.0)	<0.001
Prostatic disease/disorder	165 (19.7)	226 (17.0)	0.121
Chronic pain	155 (18.5)	211 (16.0)	0.113
Insomnia/sleep disturbance	129 (15.4)	185 (14.0)	0.342
Asthma/COPD	102 (12.2)	118 (8.9)	0.013
Headaches (within the last 2 weeks)	70 (8.4)	125 (9.4)	0.405
Rheumatoid arthritis	28 (3.3)	29 (2.2)	0.101
Osteoporosis	15 (1.8)	15 (1.1)	0.199
Not reported	0 (0.0)	4 (0.3)	nr

Risk factor/condition	*Hypogonadism prevalence rate (95% CI)*	*Odds ratio (95% CI)*
Obesity	52.4 (47.9–56.9)	2.38 (1.93–2.93)
Diabetes	50.0 (45.5–54.5)	2.09 (1.70–2.58)
Hypertension	42.4 (39.6–45.2)	1.84 (1.53–2.22)
Rheumatoid arthritis	47.3 (34.1–60.5)	1.59 (0.92–2.72)
Hyperlipidaemia	40.4 (37.6–43.3)	1.47 (1.23–1.76)
Osteoporosis	44.4 (25.5–64.7)	1.41 (0.64–3.01)
Asthma/COPD	43.5 (36.8–50.3)	1.40 (1.04–1.86)
Prostatic disease/disorder	41.3 (36.4–46.2)	1.29 (1.03–1.62)
Chronic pain	38.8 (33.7–44.0)	1.13 (0.89–1.44)
Headaches (within last 2 weeks)	32.1 (25.3–38.8)	0.81 (0.58–1.11)

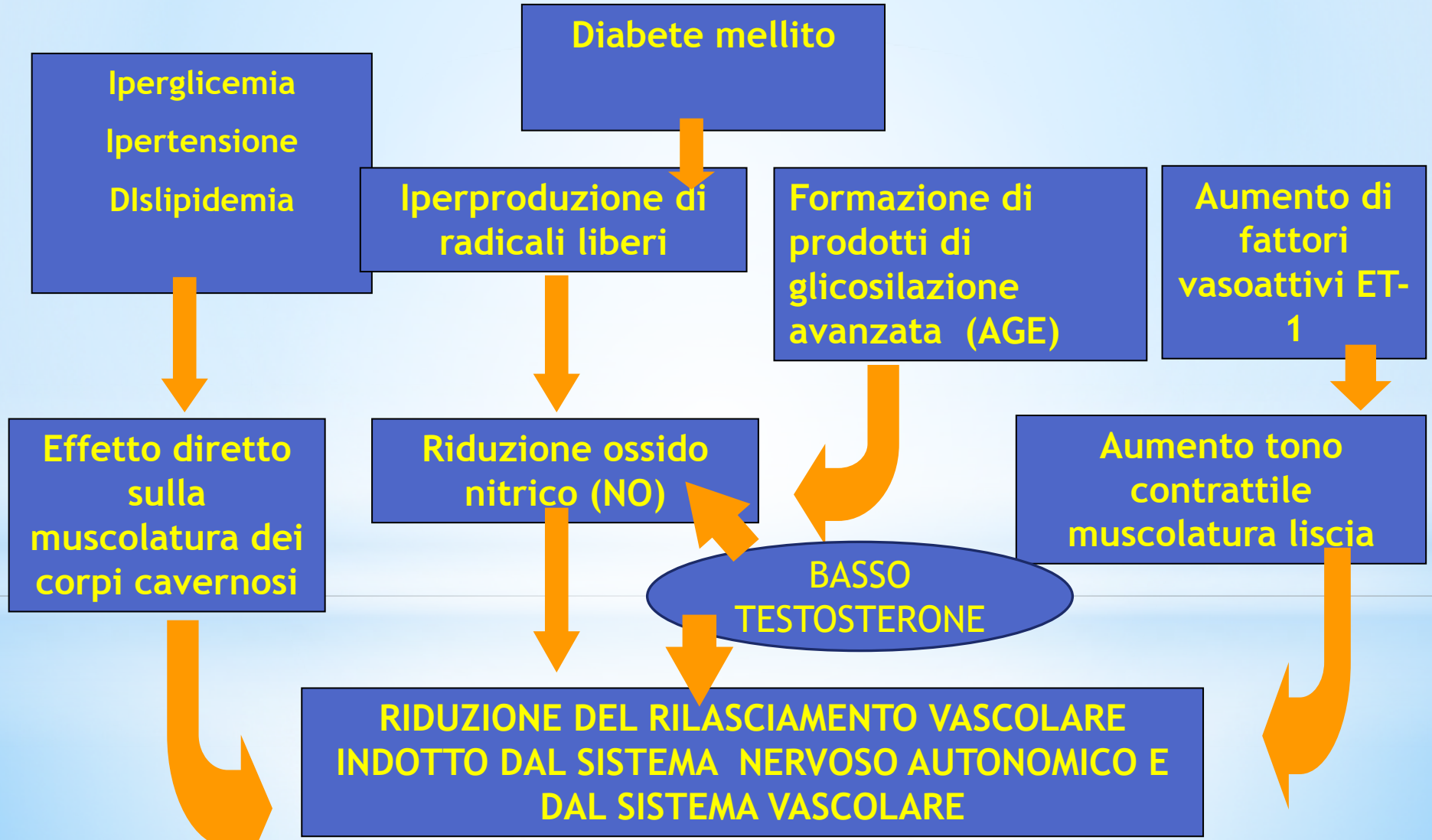
CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Link tra diabete mellito e deficit di testosterone



Saboor Aftab SA, Clin Endocrinol (Oxf) 2013 March

ETIOPATOGENESI CLASSICA DE NEL PAZIENTE DM



CLINICAL DIABETES · Volume 23, Number 3, 2005

ETIOPATOGENESI DE NEL PAZIENTE DM NUOVE TEORIE

Meccanismi patogenetici comuni

- **Riduzione del segnale NO-cGMP**
- **Aumento del segnale RhoA-ROCK**
- **Iperattività autonomica**
- **Aterosclerosi pelvica**

Conseguenze funzionalità livello tissutale (cavernosi,prostata, vescica)

- *Ridotta funzione nervosa ed endoteliale*
- *Alterato rilasciamento o contrattilità della muscolatura liscia*
- *Insufficienza arteriosa, ridotto flusso sanguigno e ipossia correlata al danno d'organo*

→ **DE**
LUTS
IPB

Infiammazione cronica

Squilibrio ormonale steroideo

Diabete, ipertensione, sindrome metabolica, ecc

Adapted from Andersson K-E et al., NeuroUrology and Urodynamics 2011;30:292-301

Asian Journal of Andrology

Asian J Androl. 2015 Jan-Feb; 17(1): 5–10.
Published online 2014 Sep 9. doi: 10.4103/1008-682X.137687
PMCID: PMC4291878

Lifestyle modifications and erectile dysfunction: what can be expected?

Maria Ida Maiorino,[1] Giuseppe Bellastella,[1] and Katherine Esposito[2]

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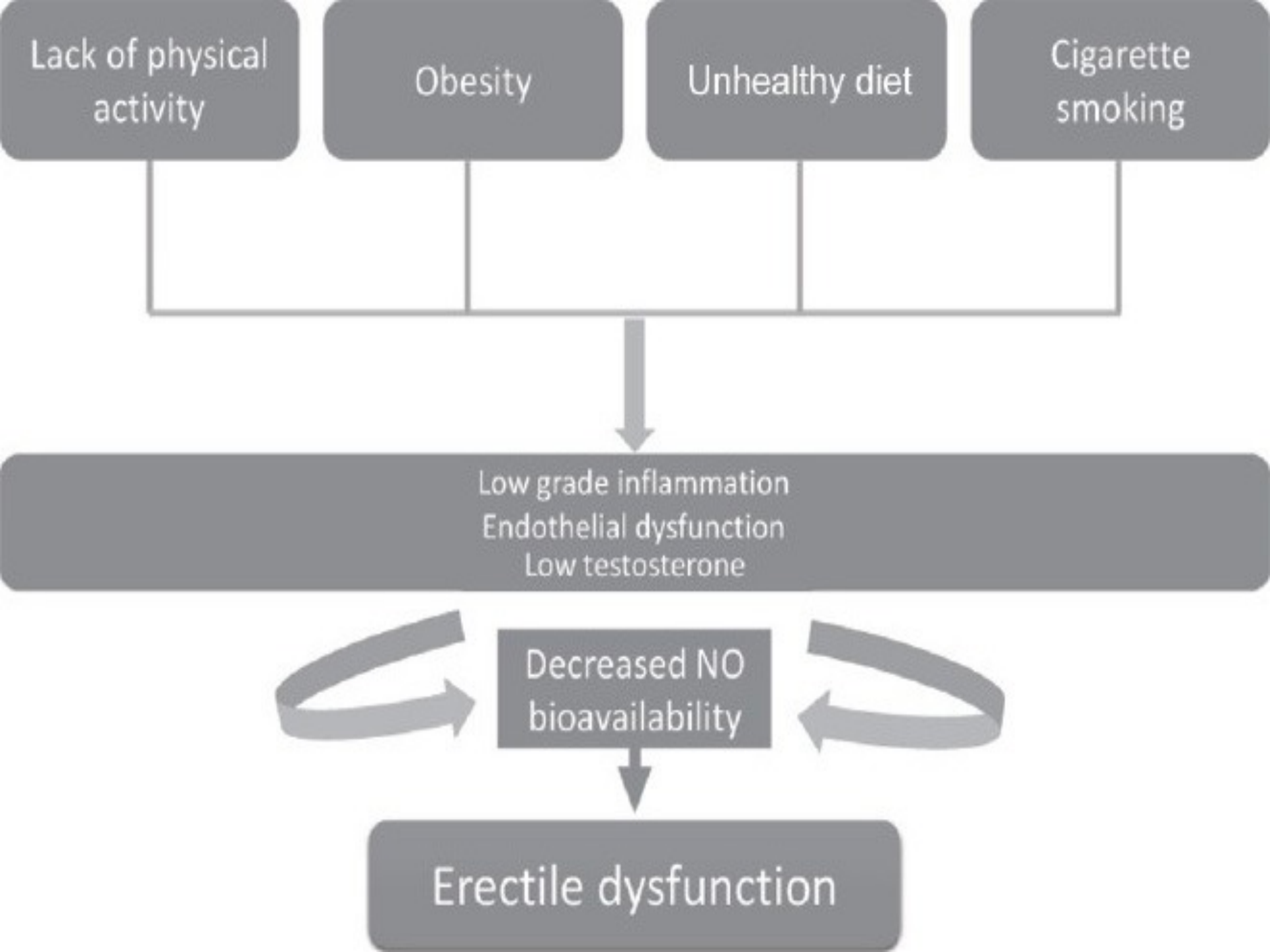
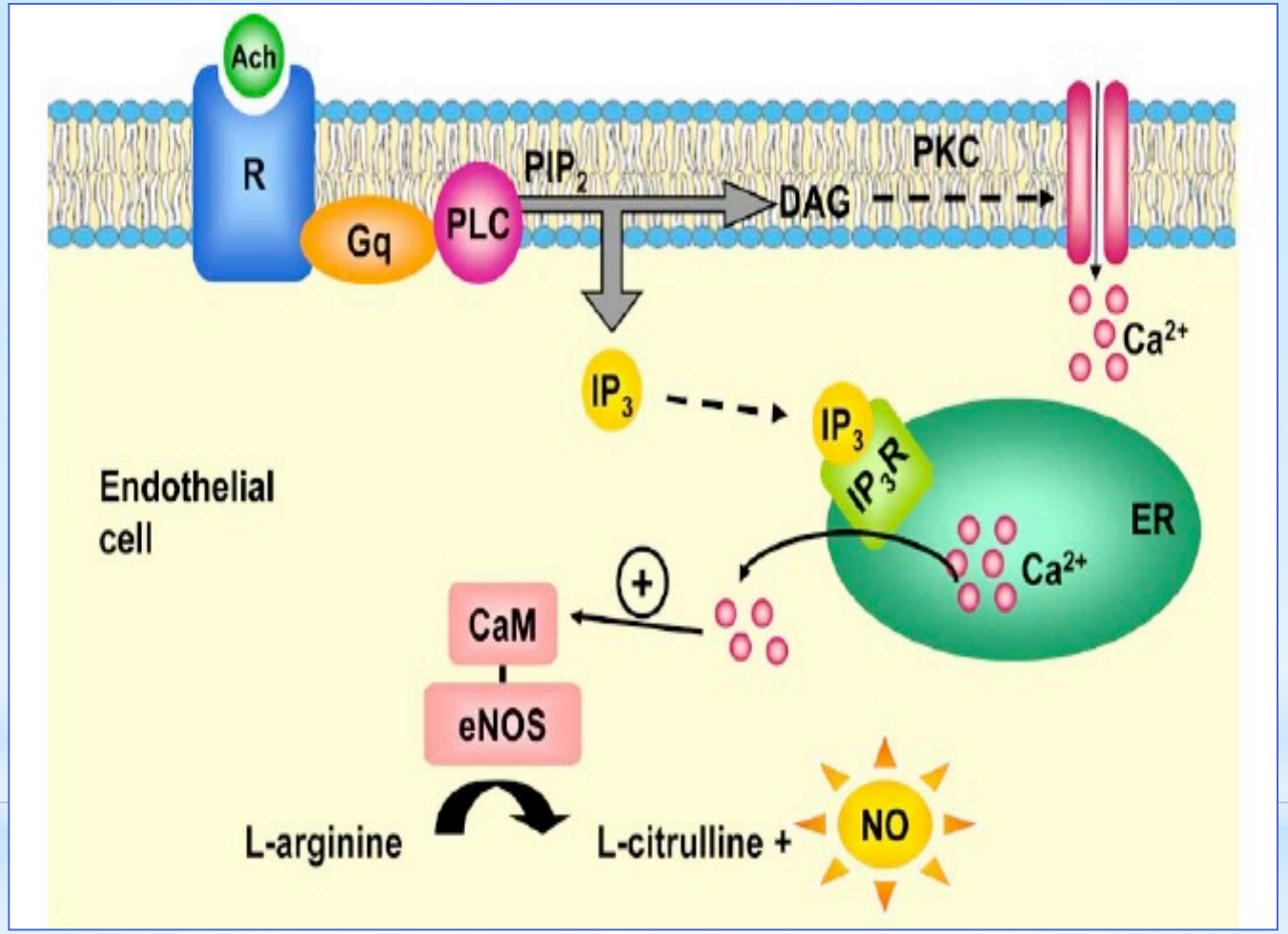
This article has been cited by other articles in PMC.

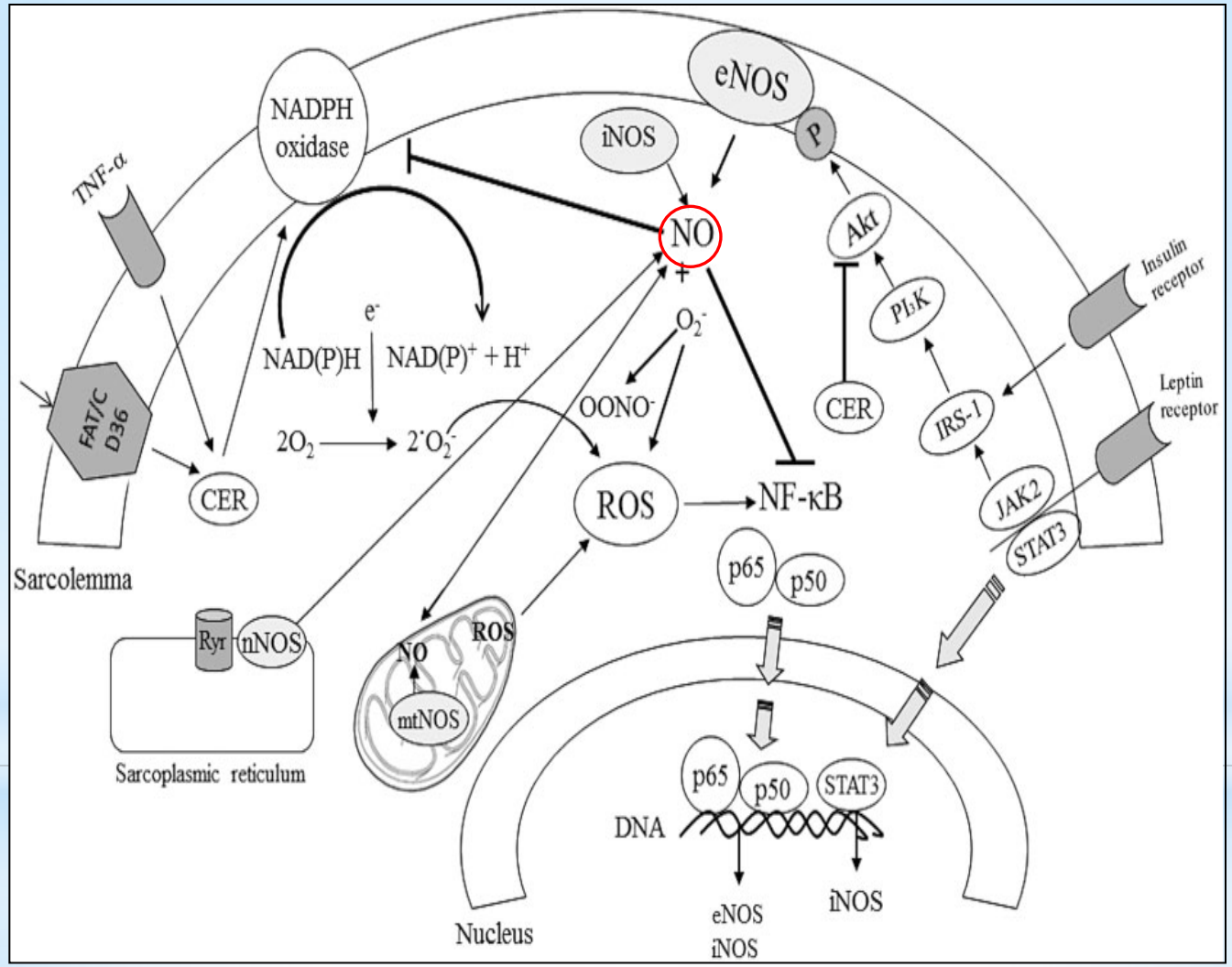

Lack of physical activity
Obesity
Unhealthy diet
Cigarette smoking
Low grade inflammation
Endothelial dysfunction
Low testosterone
Decreased NO bioavailability
Erectile dysfunction

Nitric oxide synthesis in endothelial cell



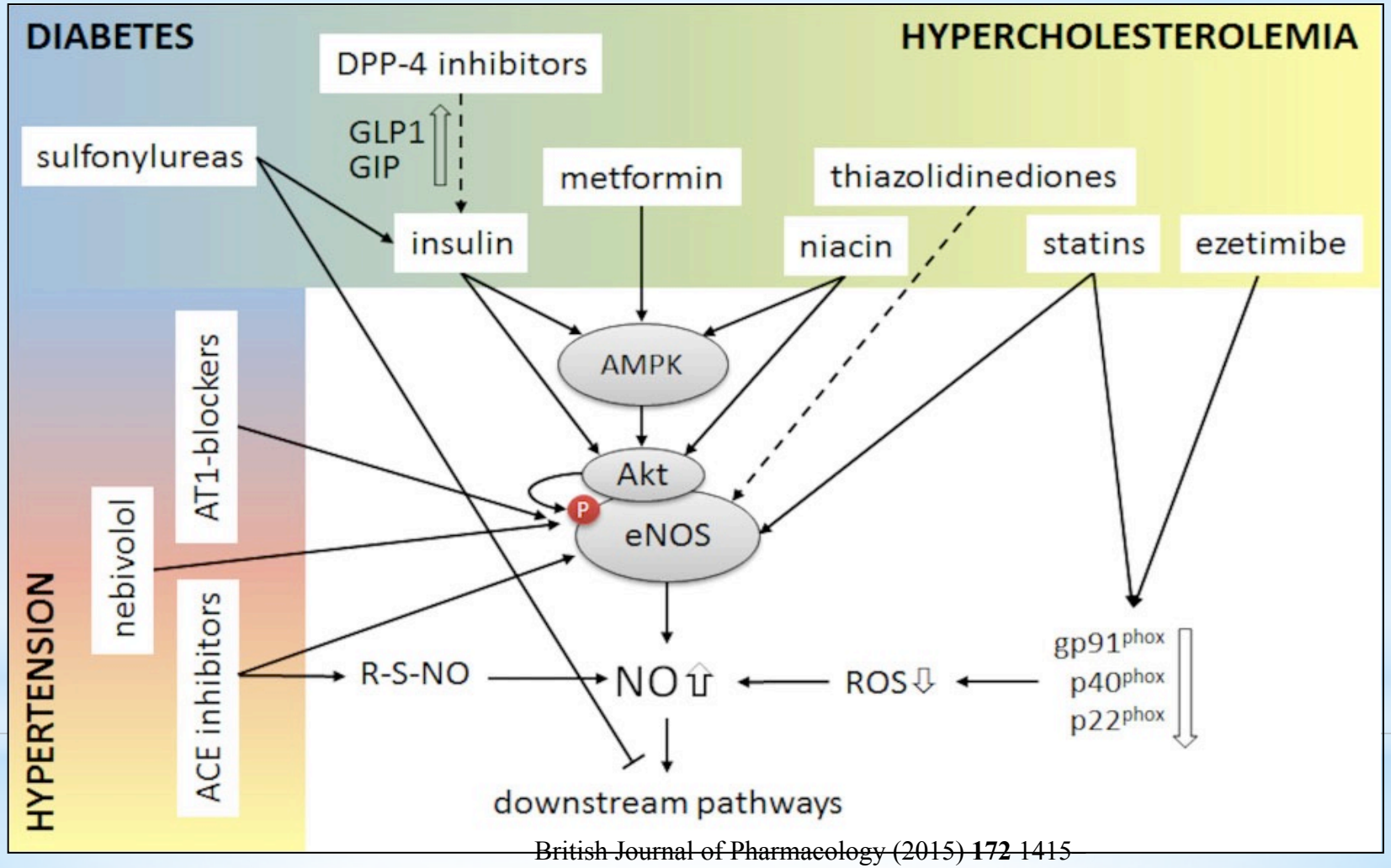
Current Vascular Pharmacology, 2010, Vol. 8, No.

NO signalling and metabolic syndrome-related pathways



British Journal of Pharmacology (2015) **172** 1415–1433 1417

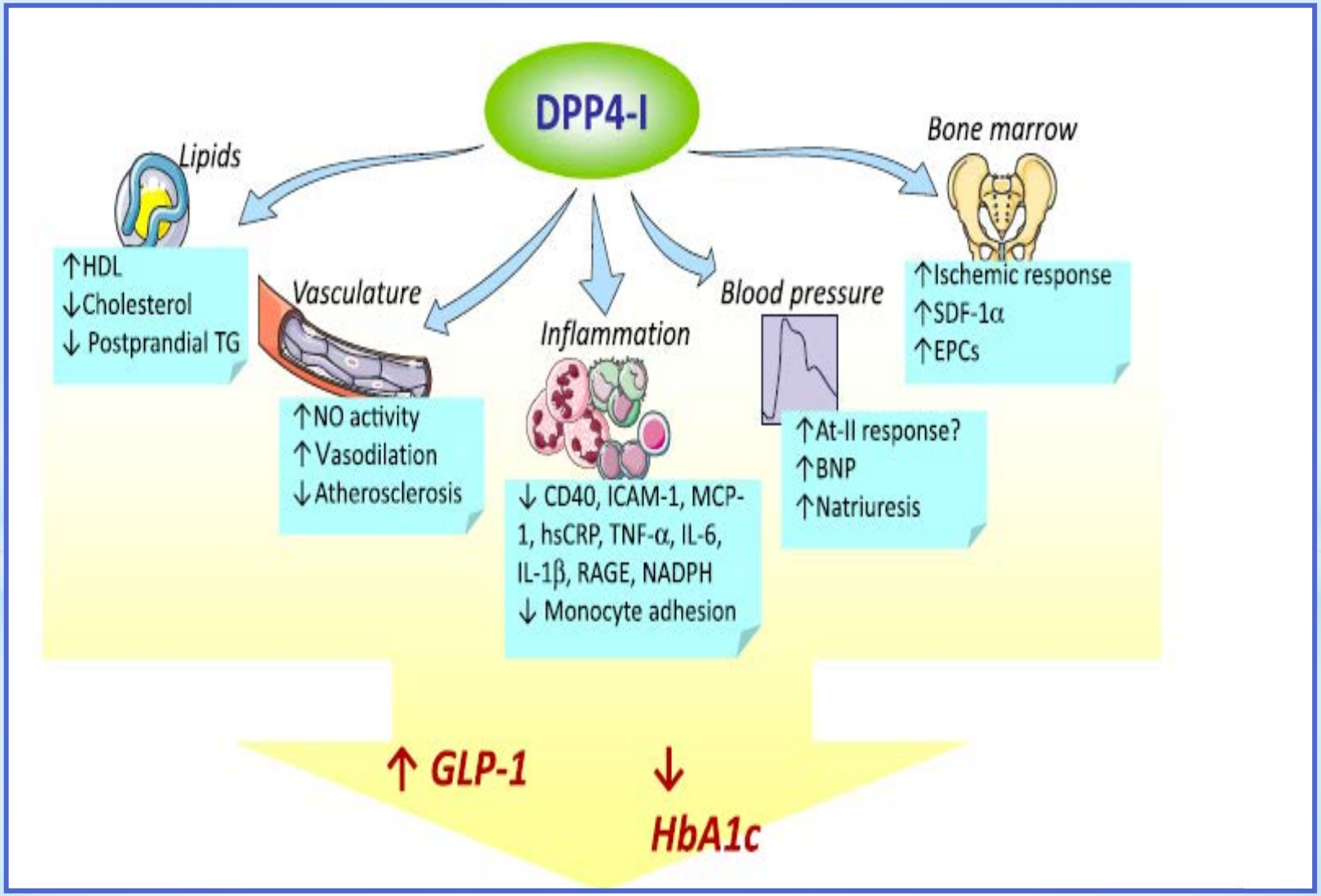
Effect of drugs used in the metabolic syndrome on cardiac NO signalling.



British Journal of Pharmacology (2015) **172** 1415
1433 1417

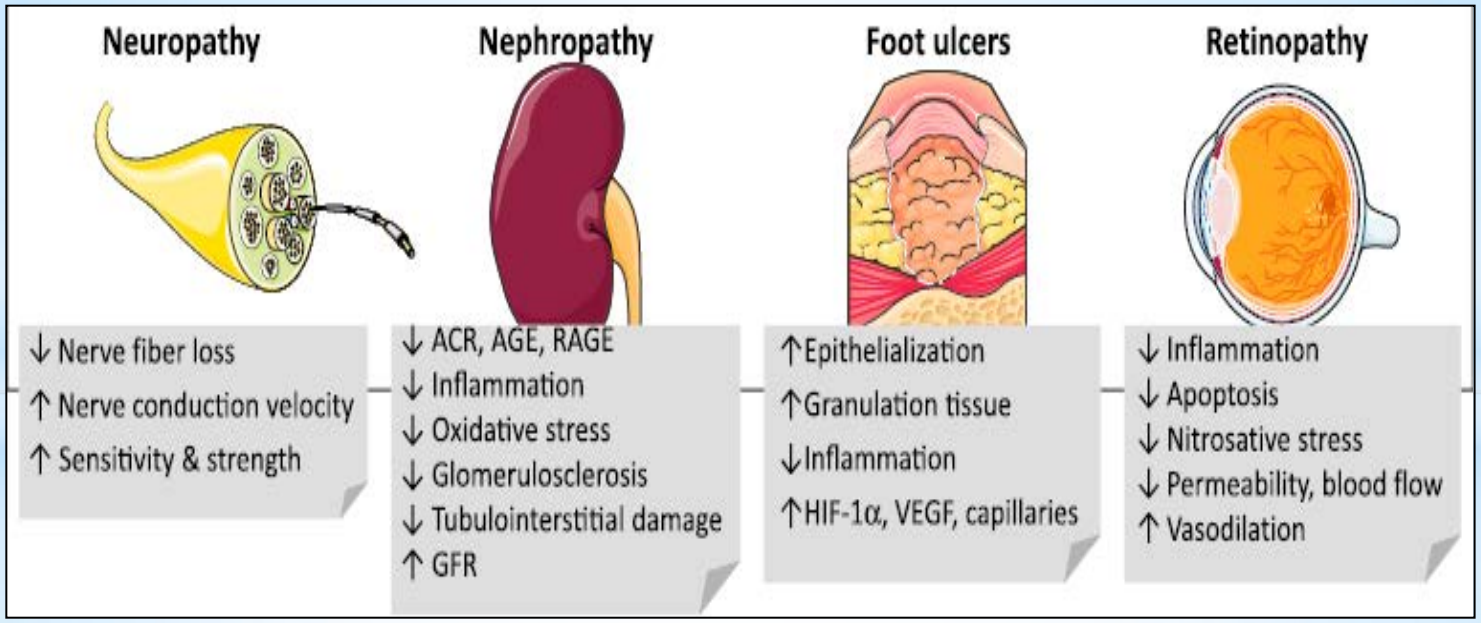
...antidiabetics (except for sulfonylureas) may positively affect tissue NO availability and NO signa thereby providing a promising tool to treat cardiac complications of the metabolic syndrome.

The roles of DPP-4 inhibition on diabetic microangiopathy



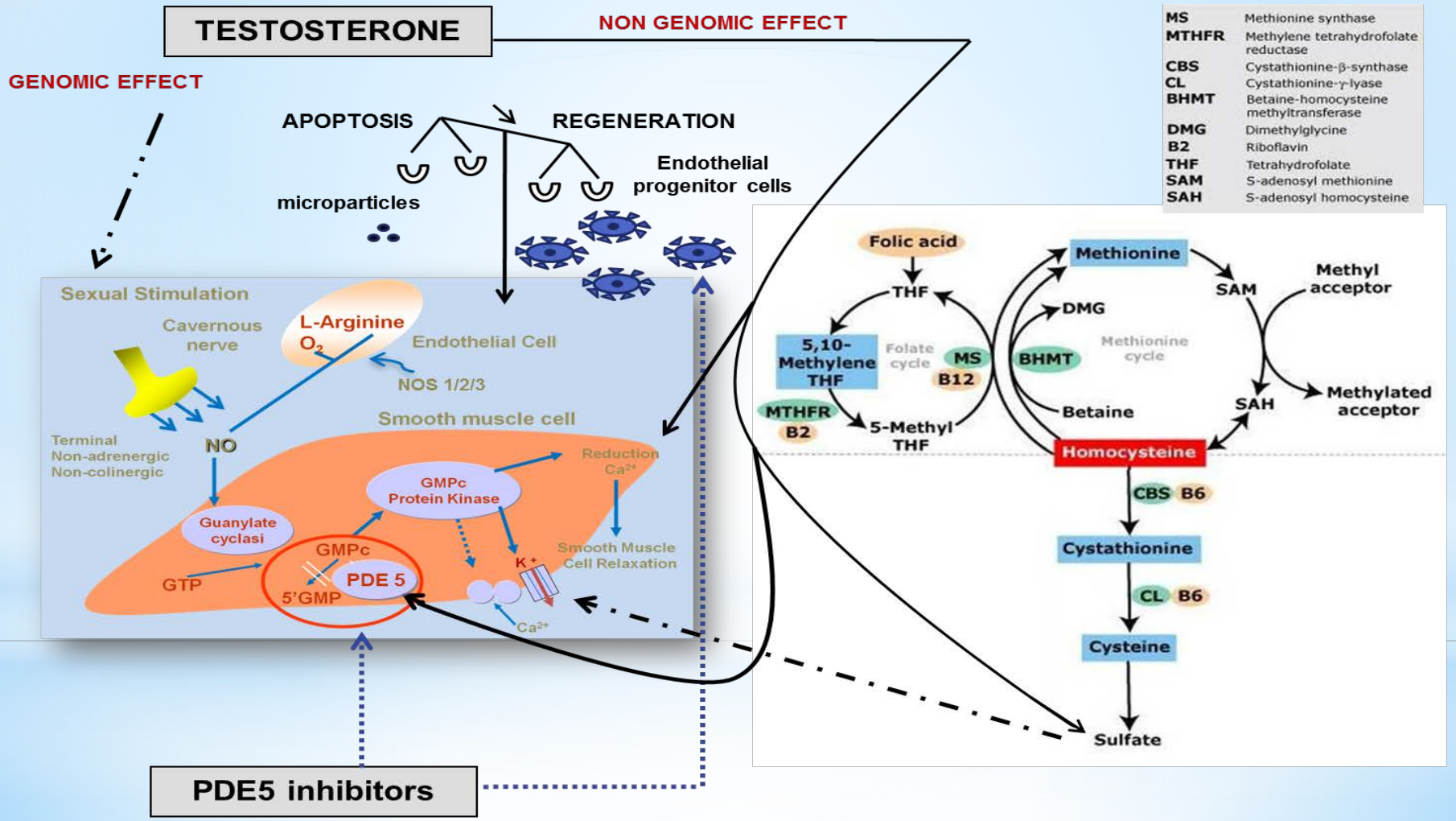
Avogaro and Fadini
Diabetes Care Volume 37, October 2014

The roles of DPP-4 inhibition on diabetic microangiopathy



Avogaro and Fadini
Diabetes Care Volume 37, October 2014

TESTOSTERONE E DE



Aversa et al, Ther Adv Urol, 2009

ANDROLOGY

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ORIGINAL ARTICLE

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Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism

[1,2]V. A. Giagulli, [3]M. D. Carbone, [1]M. I. Ramunni, [2]B. Licchelli, [4]G. De Pergola, [5]C. Sabbà, [2]E. Guastamacchia and [2]V. Triggiani

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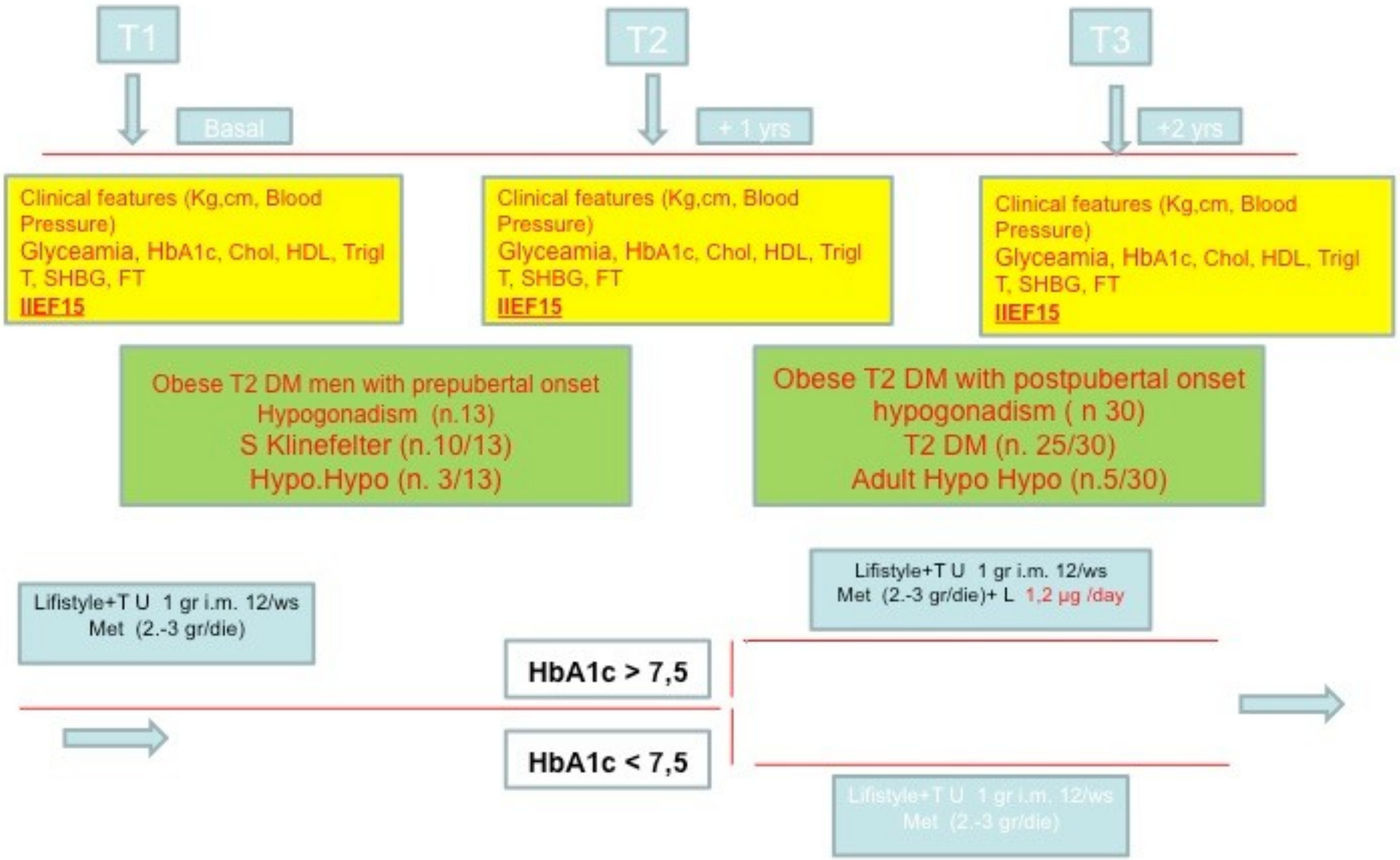
SUMMARY

The aim of this retrospective observational study was to evaluate whether adding liraglutide to lifestyle changes, metformin (Met) and testosterone replacement therapy (TRT), by means of improving weight and glycaemic control, could boost erectile function in type 2 diabetic obese men with overt hypogonadism and erectile dysfunction (ED) in a 'real-life setting'. Forty-three obese, diabetic and hypogonadal men (aged 45–59 years) were evaluated because of complaining about the recent onset of ED. They were subdivided into two groups according to whether hypogonadism occurred after puberty (G1; $n = 30$: 25 with dysfunctional hypogonadism and 5 with acquired hypogonadotropic hypogonadism) or before puberty (G2; $n = 13$: 10 with Klinefelter's syndrome and 3 with idiopathic hypogonadotropic hypogonadism). Both G1 and G2 patients were given a combination of testosterone (T) [testosterone undecanoate (TU) 1000 mg/every 12 weeks] and Met (2000–3000 mg/day) for 1 year. In the poor responders (N) to this therapy in terms of glycaemic target (G1N: $n = 16$; G2N: $n = 10$), liraglutide (L) (1.2 μg/day) was added for a second year, while the good responders (Y) to T + Met (G1Y: 14/30 and G2Y: 3/13) continued this two drugs regimen therapy for another year. All patients were asked to fill in the International Index of Erectile Function (IIEF 15) questionnaire before starting TU plus Met (T1) and after 12 months (T2) and 24 months (T3) of treatment. Patients underwent a clinical examination and a determination of serum sex hormone binding globulin (SHBG), total testosterone (T) and glycosylated haemoglobin (HbA1c) at T1, T2 and T3. At T2, each patient obtained an improvement of ED ($p < 0.01$) and of the metabolic parameters without reaching, however, the glycaemic goals [HbA1c = >7.5% (>58 mmol/mol)], while T turned out to be within the range of young men. L added to TU and Met regimen in G1N and G2N allowed these patients to reach not only the glycaemic target [HbA1c = <7.5% (<58 mmol/mol)] and a significant reduction in body weight ($p < 0.01$), but also a further increase in SHBG ($p < 0.05$) and T ($p < 0.01$) plasma levels as well as a significant increment of IIEF score (T3). Conversely, at T3 G1Y and G2Y, who received the combined therapy with TRT and Met for the second year, showed a partial failure of that treatment given that there was no improvement of the IIEF score and they showed a significant rise in serum HbA1c ($p < 0.05$) and weight ($p < 0.04$) compared with the assessments at T2. These results suggest that TRT could improve clinical and metabolic parameters in obese, type 2 diabetic men with ED and overt hypogonadism (independently of when T deficit occurred). Furthermore, in case of insufficient metabolic control the addition of L to TRT and Met regimen allows to achieve serum T levels in the range of healthy men, as well as to reach glycaemic target and to lower weight, leading to a considerable improvement of ED.

Participants, setting, design overview and therapeutic strategy



Clinical characteristics , metabolic parameters and hormonal levels in obese T2DM men with hypogonadism treated with TU and Met for 1 yr

	Postpubertal onset (n30)		Prepubertal onset (n13)	
	T1	T2	T1	T2
Age (yrs)	53,5± 4,4		50,6±4,3	
BMI	34,2±2,3	32,5±1,9 *	34,7±2,3	33,5±33,5 *
Waist (cm)	105,1±10,3	102,1±8,5 **	105,1±10,3	102,1±9,4 **
Glyc (mg/dl)	184,5±31	162,1±20,5 ***	184,4±31	162,1±20,4 **
HbA1c %	8,8±0,6	7,8±0,6 **	8,6±0,4	7,9±0,4 **
T (ng/dl)	278,4±23,7	464,3±63,5 ***	309,4±29,7	412,3±47,5 ***
SHBG (nMol/l	36,3±2,7	37,3±3,4 *	36,6±2,7	37,6±2,4 *
FT (ng/dl)	5,2±0,6	8,7±1,5 ***	5,8±0,7	7,7±1,2 ***
IIEF 15	12,2±2,3	14,4±1,8**	14,0±2,0	16,3±3,2 **

*p <0,05
**p >0,01
*** p> 0,001

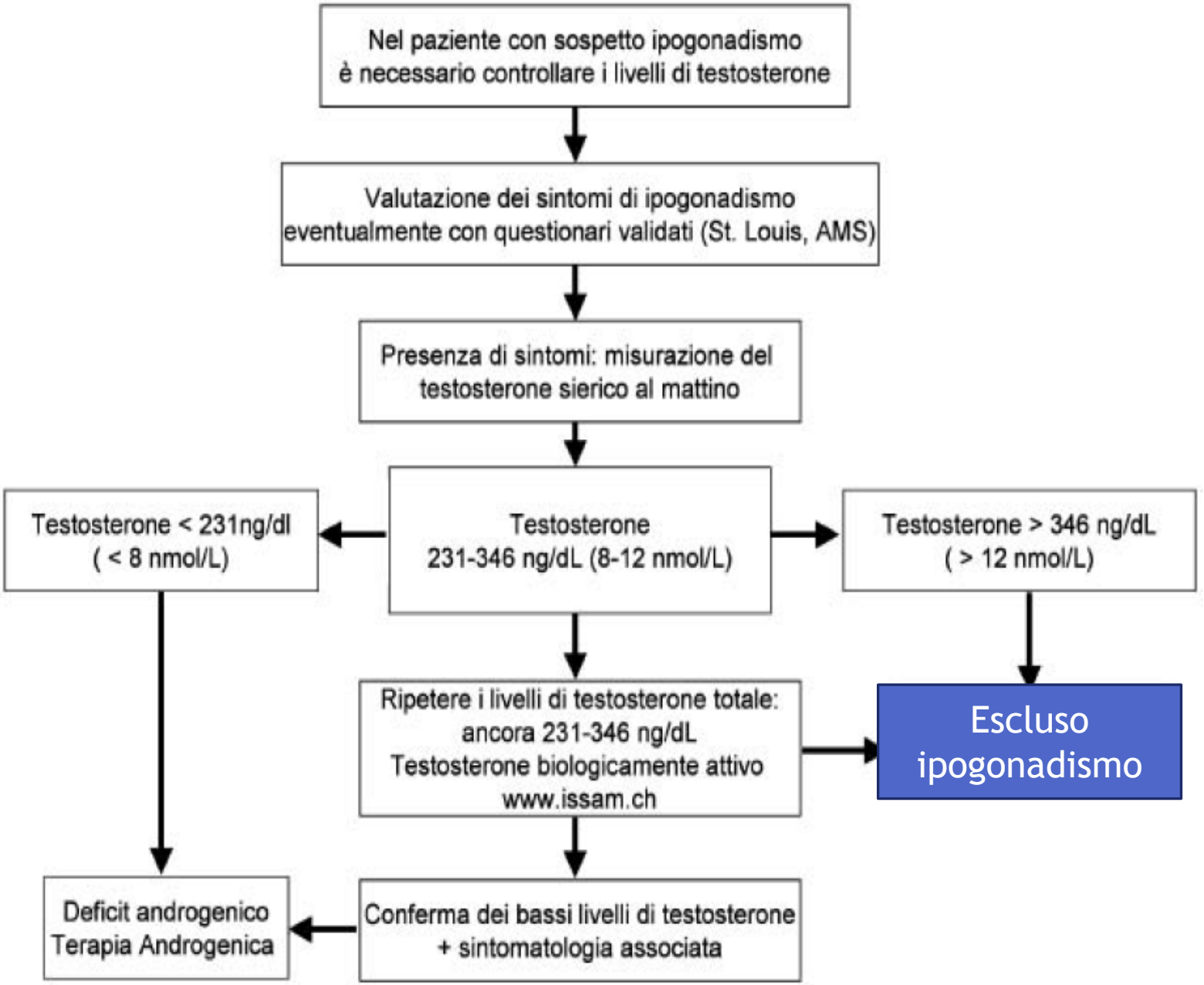
Clinical characteristics , metabolic parameters and hormonal levels of subgroup of poor responders among the post-pubertal onsent hypogonadal men (n 16)

	T1	T2	T1
Age (yrs)	52,5± 4,5		
BMI	35,2±2,3	34,±3,2 *	32,6±2,0 **
Waist (cm)	103,7±7,0	100,1±6,5 **	92,1±5,3 ***
Glyc (mg/dl)	180,4±25	155,1±20,0 ***	130,4±16 ***
HbA1c %	9,1±0,4	8,5±0,3 **	7,3±0, ***
T (ng/dl)	282,4±25,0	466,3±63,5 ***	481,7±57,3 ***
SHBG (nMol/l	36,0±3,2	37,3±3,4 *	39,1±2,2 **
FT (ng/dl)	5,4±0,6	8,7±1,6 ***	9,0±1,3
IIEF 15	12,2±2,2	14,6±1,7*	19,9±2,0 ***

*p <0,05
**p >0,01
*** p> 0,001

SUMMARY

The aim of this retrospective observational study was to evaluate whether adding liraglutide to lifestyle changes, metformin (Met) and testosterone replacement therapy (TRT), by means of improving weight and glycaemic control, could boost erectile function in type 2 diabetic obese men with overt hypogonadism and erectile dysfunction (ED) in a 'real-life setting'. Forty-three obese, diabetic and hypogonadal men (aged 45–59 years) were evaluated because of complaining about the recent onset of ED. They were subdivided into two groups according to whether hypogonadism occurred after puberty (G1; $n = 30$: 25 with dysfunctional hypogonadism and 5 with acquired hypogonadotropic hypogonadism) or before puberty (G2; $n = 13$: 10 with Klinefelter's syndrome and 3 with idiopathic hypogonadotropic hypogonadism). Both G1 and G2 patients were given a combination of testosterone (T) [testosterone undecanoate (TU) 1000 mg/every 12 weeks] and Met (2000–3000 mg/day) for 1 year. In the poor responders (N) to this therapy in terms of glycaemic target (G1N: $n = 16$; G2N: $n = 10$), liraglutide (L) (1.2 μg/day) was added for a second year, while the good responders (Y) to T + Met (G1Y: 14/30 and G2Y: 3/13) continued this two drugs regimen therapy for another year. All patients were asked to fill in the International Index of Erectile Function (IIEF 15) questionnaire before starting TU plus Met (T1) and after 12 months (T2) and 24 months (T3) of treatment. Patients underwent a clinical examination and a determination of serum sex hormone binding globulin (SHBG), total testosterone (T) and glycosylated haemoglobin (HbA1c) at T1, T2 and T3. At T2, each patient obtained an improvement of ED ($p < 0.01$) and of the metabolic parameters without reaching, however, the glycaemic goals [HbA1c = >7.5% (>58 mmol/mol)], while T turned out to be within the range of young men. L added to TU and Met regimen in G1N and G2N allowed these patients to reach not only the glycaemic target [HbA1c = <7.5% (<58 nmol/mol)] and a significant reduction in body weight ($p < 0.01$), but also a further increase in SHBG ($p < 0.05$) and T ($p < 0.01$) plasma levels as well as a significant increment of IIEF score (T3). Conversely, at T3 G1Y and G2Y, who received the combined therapy with TRT and Met for the second year, showed a partial failure of that treatment given that there was no improvement of the IIEF score and they showed a significant rise in serum HbA1c ($p < 0.05$) and weight ($p < 0.04$) compared with the assessments at T2. These results suggest that TRT could improve clinical and metabolic parameters in obese, type 2 diabetic men with ED and overt hypogonadism (independently of when T deficit occurred). Furthermore, in case of insufficient metabolic control the addition of L to TRT and Met regimen allows to achieve serum T levels in the range of healthy men, as well as to reach glycaemic target and to lower weight, leading to a considerable improvement of ED.


Nel paziente con sospetto ipogonadismo
è necessario controllare i livelli di testosterone
Valutazione dei sintomi di ipogonadismo
eventualmente con questionari validati (St. Louis, AMS)
Presenza di sintomi: misurazione del
testosterone sierico al mattino
Testosterone < 231ng/dl
(< 8 nmol/L)
Testosterone
231-346 ng/dL (8-12 nmol/L)
Testosterone > 346 ng/dL
(> 12 nmol/L)
Ripetere i livelli di testosterone totale:
ancora 231-346 ng/dL
Testosterone biologicamente attivo
www.issam.ch
Escluso
ipogonadismo
Deficit androgenico
Terapia Androgenica
Conferma dei bassi livelli di testosterone
+ sintomatologia associata

[Regulatory effect of liraglutide on the expression of eNOS in the corpus cavernosum of diabetic rats].

Yue L, et al. Zhonghua Nan Ke Xue. 2016. Show full citation

Abstract

OCTOBER: To explore the effects of the glucagon-like peptide 1 (GLP-1) liraglutide on the penile erectile function of rats with diabetic erectile dysfunction (DED) by observing the impact of liraglutide on the expression of eNOS in the corpus cavernosum of diabetic rats.

METHODS: We randomly divided 30 six-week-old male SD rats into a normal control (n = 10) and an experimental group (n = 20) , established models of diabetes mellitus (DM) in the experimental rats, and subdivided them into a DM (n = 8) and a GLP-1 group (n = 8) to receive intramuscular injection of normal saline and liraglutide at 5 mg per kg of the body weight per day, respectively. After 12 weeks of intervention, we obtained the levels of FPG, FINS, TG, TC, HDL-C, LDL-C, testosterone, and IL-6 and the indexes of Homa-IR and Homa-β, detected the expressions of Akt/p-Akt and eNOS/p-eNOS in the corpus cavernosum by Western blot, and compared the erectile function between different groups.

RESULTS: The frequency and rate of penile erection were significantly lower in the DM group than in the GLP-1 and normal control groups ($P < 0.05$) and also lower in the GLP-1 group than in the normal controls ($P < 0.05$). Immunofluorescence staining showed the expression of eNOS mainly in the cytoplasm of the cavernosal vessels and sinusoidal endothelial cells, markedly lower in the DM and GLP-1 groups than in the normal rats ($P < 0.05$), but higher in the GLP-1 than in the DM group ($P < 0.05$). The level of eNOS/p-eNOS in the penile tissue was significantly decreased in the DM and GLP-1 groups in comparison with the normal controls ($P < 0.01$ or $P < 0.05$), while that of p-eNOS was markedly increased in the GLP-1 group as compared with the DM group ($P < 0.05$). No statistically significant differences were observed in the Akt level among the three groups of animals ($P > 0.05$). The expression of p-Akt was remarkably reduced in the DM and GLP-1 groups in comparison with the control rats ($P < 0.01$ or $P < 0.05$), but higher in the GLP-1 than in the DM group ($P < 0.05$). CONCLUSION: GLP-1 can protect the function of endothelial cells in the corpus cavernosum and improve the erectil function of DED rats by regulating the Akt/eNOS signaling pathway,witch indicates that GLP1 could be an important option for the treatment and prevention of DED

Studio prospettico osservazionale nel paziente diabetico con Disfunzione erettile e/o ipogonadismo e/o sintomi delle basse vie urinarie
GRUPPO DI STUDIO DIABETE e ANDROLOGIA AMD

INTRODUZIONE:
Recenti studi hanno evidenziato che la disfunzione erettile (DE) presenta lo stesso meccanismo patogenetico dei sintomi delle basse vie urinarie (o lower urinary tract symptoms in sigla LUTS) attraverso un' attivazione della via RhoA/RhoAkinase e che entrambi presentano le stesse comorbidità (diabete mellito, sindrome metabolica,ipertensione arteriosa, dislipidemia) . Il trattamento sia della DE che dei LUTS non può prescindere da una valutazione dello stato della funzione gonadica essendo entrambi gli organi un bersaglio del testosterone. La riduzione età correlata della funzione testicolare con riduzione dei valori del testosterone totale, identificata nosologicamente dall' ipogonadismo dell' età adulta (Late Onset Hypogonadism, LOH), aggrava sia la DE che il metabolismo glucidico e lipidico a causa dell'aumento della massa grassa e riduzione della massa magra con peggioramento dell' insulinoresistenza.

Criteri di inclusione

Età tra i 40-65 anni
DM (criteri International Diabetes Federetion)
AMS q * > 30 totale sexual sub scale > 5
Testosterone totale <12 nmol/L **
IPSS *** <13
IIEF-5 **** < 25

* AMS questionario;
**Nei pazienti obesi conferma formula di Vermeulen (www.issam.ch/AMS_English_Evaluation.pdf), con cut-off inferiore a 250 pmol/L (10 pg/ml) ;
*** Questionario International Prostate Symptoms Score
**** International Index Erectile Function

Criteri di esclusione

Terapia con androgeni o steroidi	Iperprolattinemia o altra patologia ipotalamo-ipofisaria
Sospetto o diagnosi *di K prostatico e/o K mammario*	Grave insufficienza cardiaca, epatica o renale
OSAS non in trattamento con cPAP, policitemia, valori di Hct > 52%	Desiderio di prole
Ipertrofia prostatica benigna con IPSS > 13	Malattia psichiatrica grave
PSA > 4 ng/ml	

DISEGNO DELLO STUDIO

ARRUOLAMENTO → **START** → **CONTROLLO**

- ANAMNESI FARMACOLOGICA
- DOSAGGI ORMONALI*
- IPSS, IIEF-5, AMSq
- ECOGRAFIA PROSTATICA SOVRAPUBICA
- ECD PENIENO BASALE E DINAMICO

*LH.PRL,testosterone totale,SHBG,protidogramma,PSA libero e totale,EMOCROMO

6 mesi

- ANAMNESI FARMACOLOGICA
- DOSAGGI ORMONALI*
- IPSS, IIEF-5, AMSq

Obiettivi primari:
Valutare nella popolazione diabetica maschile che giunge negli ambulatori territoriali di diabetologia la prevalenza dei disturbi della basse vie urinarie, della disfunzione erettile e/o dell'ipogonadismo e l'eventuale loro coestistenza .

Obiettivi secondari:
Valutare la possibilità di un approccio diagnostico-terapeutico integrato nell' ambito del TEAM diabetologico da parte del medico diabetologo con esperienza professionale in andrologia clinica.

CARATTERISTICHE DEMOGRAFICHE DEI PAZIENTI
da gennaio 2015

Nr PAZIENTI: 43

ETA': 55± 6,1

DIAGNOSI DI DM2

DURATA DELLA MALATTIA: 9,95 ± 3,9

HbA1C: 7,93 ± 0,91 %

IPSS: 10,6 ± 1,84

IIEF-5: 13,8 ± 3,2

AMSq: 45 ± 15 totale sexual sub scale 10 ± 4

Testo totale pg/ml : 9,8 ± 1,7

PSA TOTALE: 0,9 ± 0,4

TERAPIA DM2	PZ
MET+ SU	8
MET+ DDPIVinh	16
MET+ DDPIVinh+ SU	4
GLP1 combo	7
MET+ INSULINA BASALE	6
INSULINA BASAL BOLUS	2

GRAZIE
PER L'ATTENZIONE