PRIMO CONGRESSO INTERREGIONALE AME SUD-ITALIA

INOSITOLO E INSULINORESISTENZA :

QUALI EVIDENZE ?

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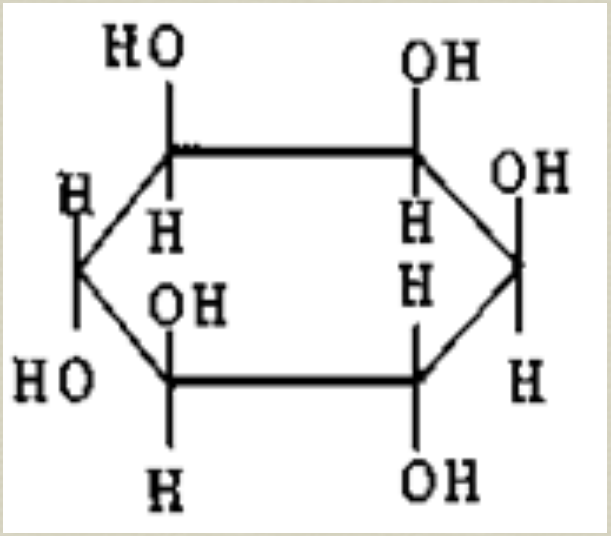
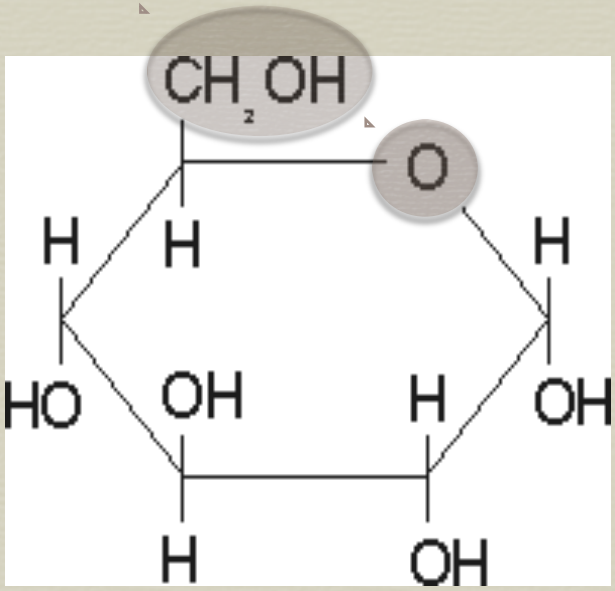
HILTON GARDEN INN Matera, 9-10 Maggio 2014

STRUTTURA CHIMICA



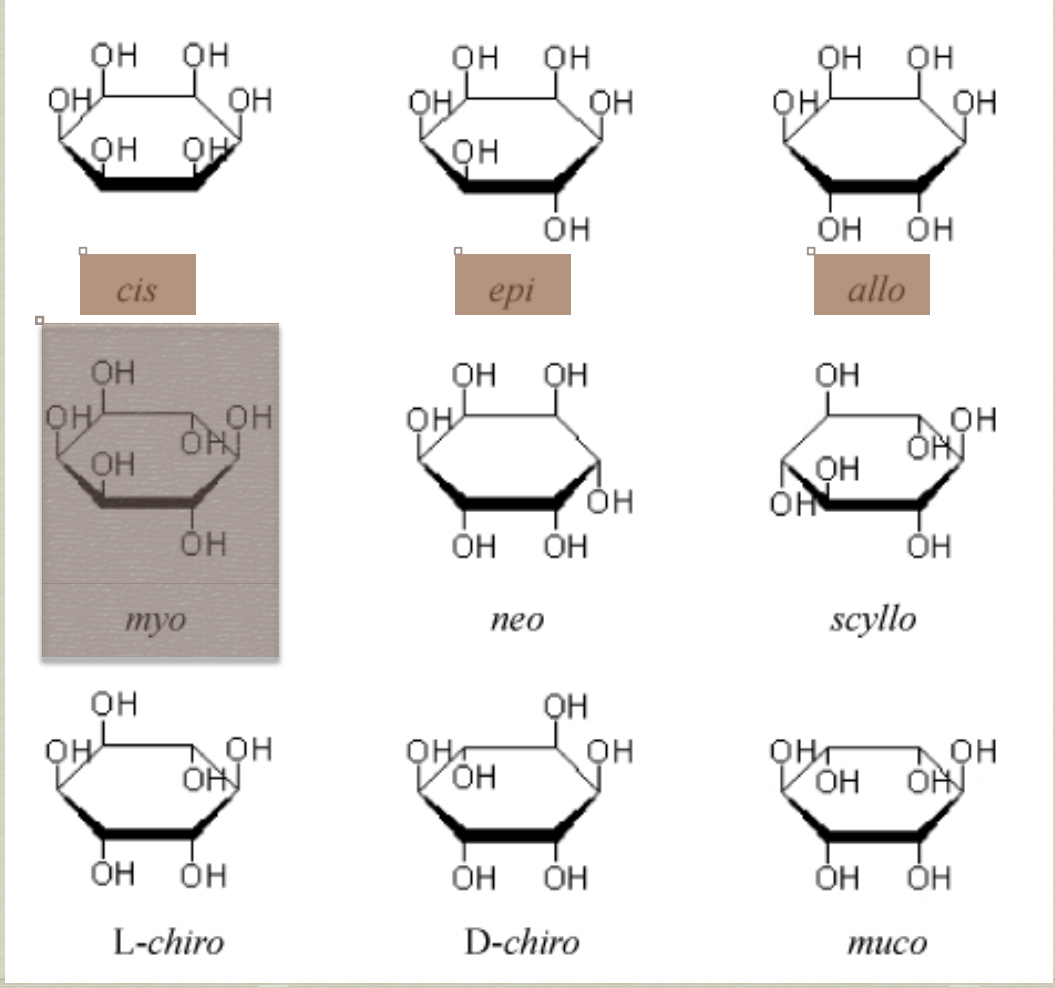
INOSITOLO
($C_6H_{12}O_6$)



GLUCOSIO
($C_6H_{12}O_6$)

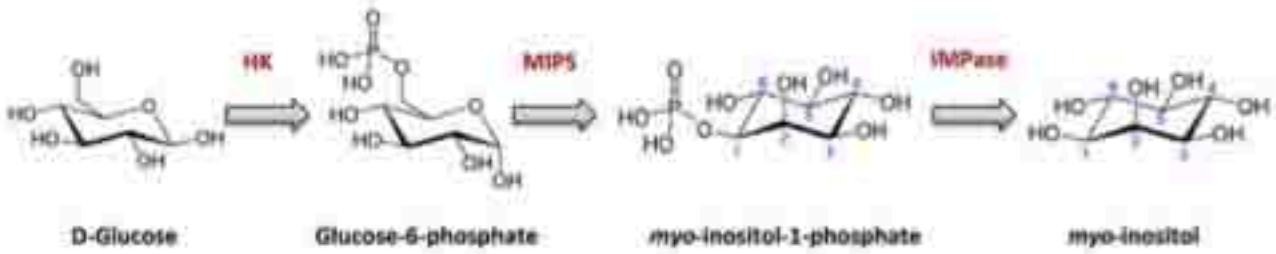
"POLIALCOL O POLIOLO CARBOCICLICO
o POLI-IDROSSI-CICLO-ALCANO"

STEREOISOMERIA

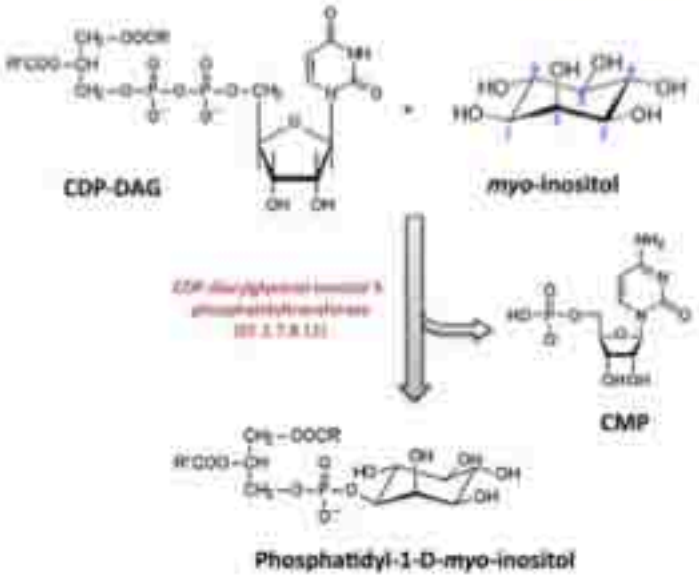


Fonti particolarmente ricche di inositolo (per 100 g di prodotto)

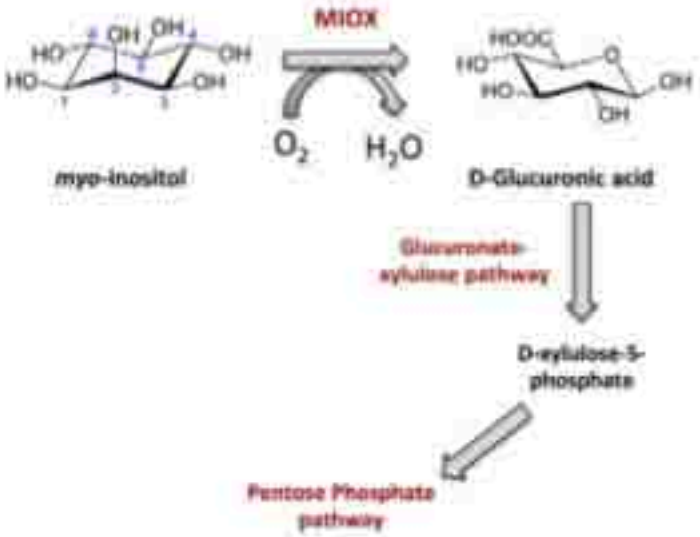
Germe di grano	690 mg
Prugne secche	470 mg
Fegato di manzo	340 mg
Riso integrale	330 mg
Fiocchi d'avena	320 mg
Noci	180 mg
Melone	170 mg
Arancia	150 mg
Banana	120 mg



MI de novo BIOSYNTHESIS from D-glucose



PHOSPHATIDYLINOSITOL synthesis from MI



MI CATABOLISM in kidney

THREE SOURCES

(1) De novo biosynthesis from glucose-6-phosphate by 1-D-myo-inositol- phosphate synthase (MIPS) and inositol monophosphatase (IMPase),

(2) Dephosphorylation of inositol phosphates derived from breakdown of inositol-containing membrane phospholipids;

(3) Or uptake from the extracellular fluid via specialized myo- inositol transporters.

   (1) H^+-myo-inositol transporte (HMIT)

   (2) Sodium-dependent myo-inositol transporters 1 and 2 (SMIT 1/2)

Myo-Inositolo

- Forma libera
- Inositolo trifosfato (IP3)
- Fosfatidil-Inositolo (PI)
- Fosfatidil-inositolo fosfato (PIP_2 / PIP_3)
- Glicani dell'inositolo
- GPI (Glicosilfosfatidilinositolo)
- Inositol Fosfoglicani (IPGs)

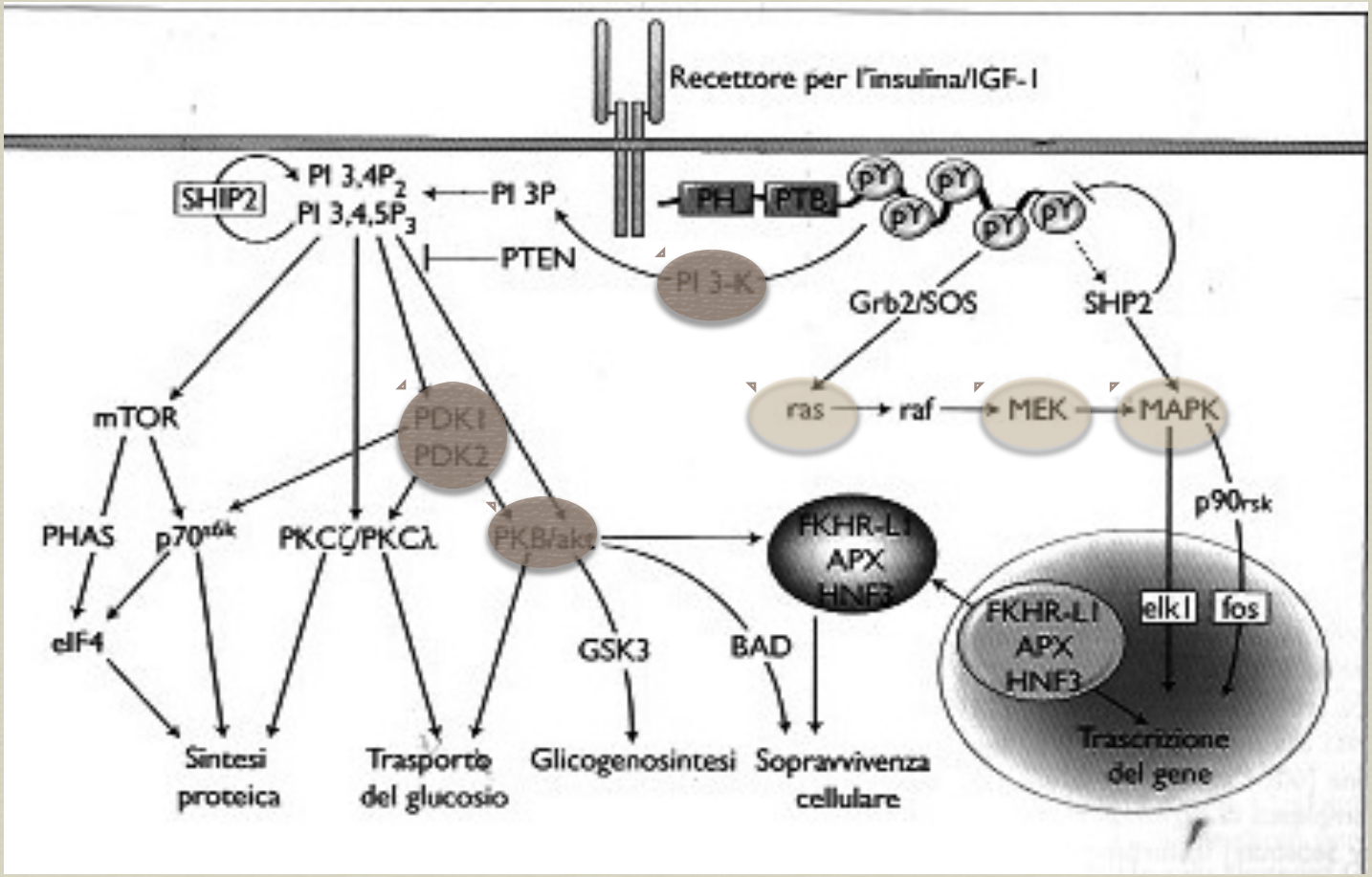
Inositol Phospho Glycan (IPGs)

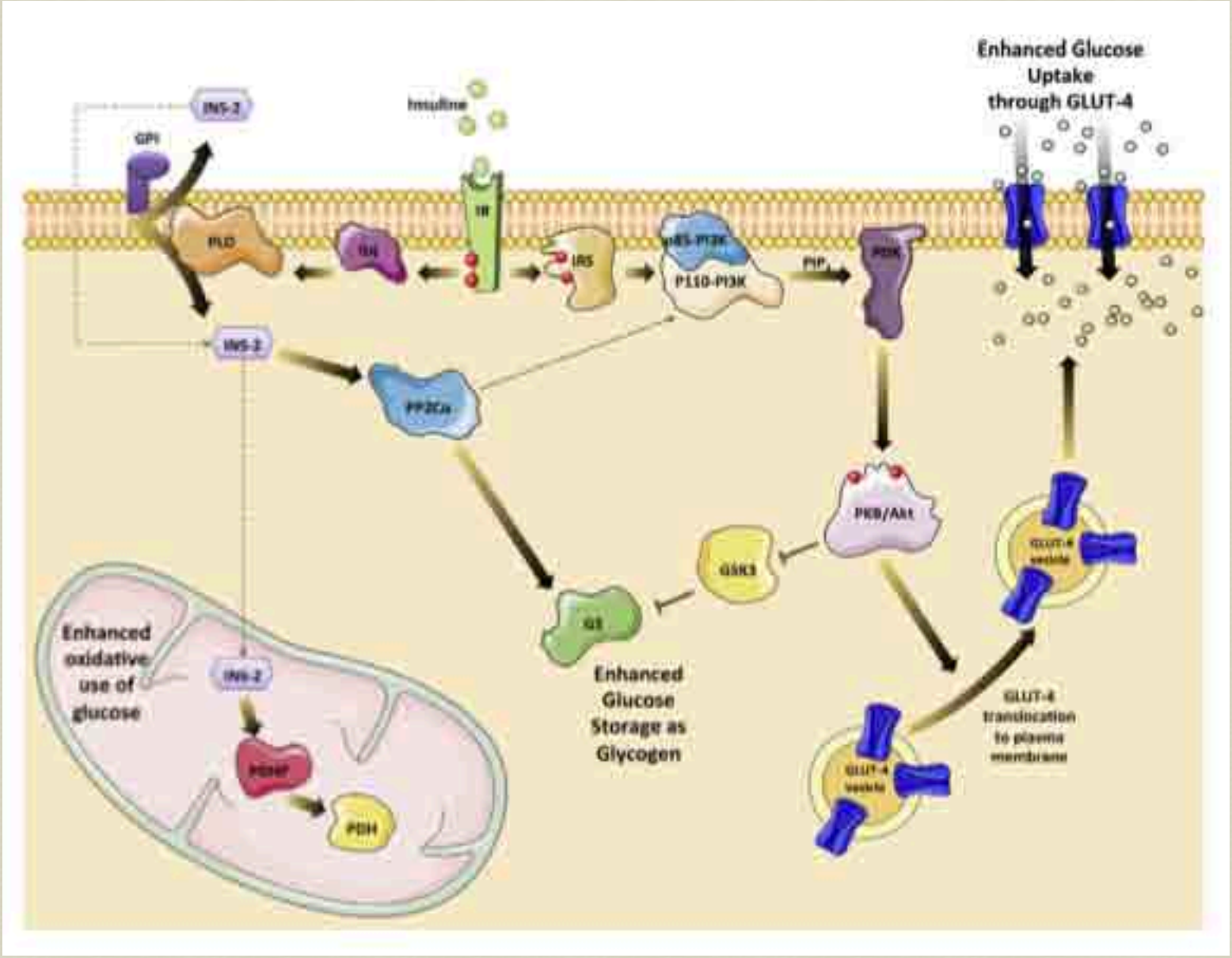
- Vengono rilasciati in risposta al legame dell'insulina al proprio recettore e derivano dall'idrolisi del GlicosilFosfatidilInositolo (GPI) presente a livello della membrana plasmatica.

- IPG-P : Galattosammina + DCI metilato (pinitolo). Attiva la PDHP e quindi la PDH e quindi l'ossidazione del piruvato ad acetil-CoA.

- IPG-A : Glucosammina + MI . Inibisce la PKA c-AMP dipendente e l'Adenilato Ciclasi (AC) e quindi la glicogenolisi.

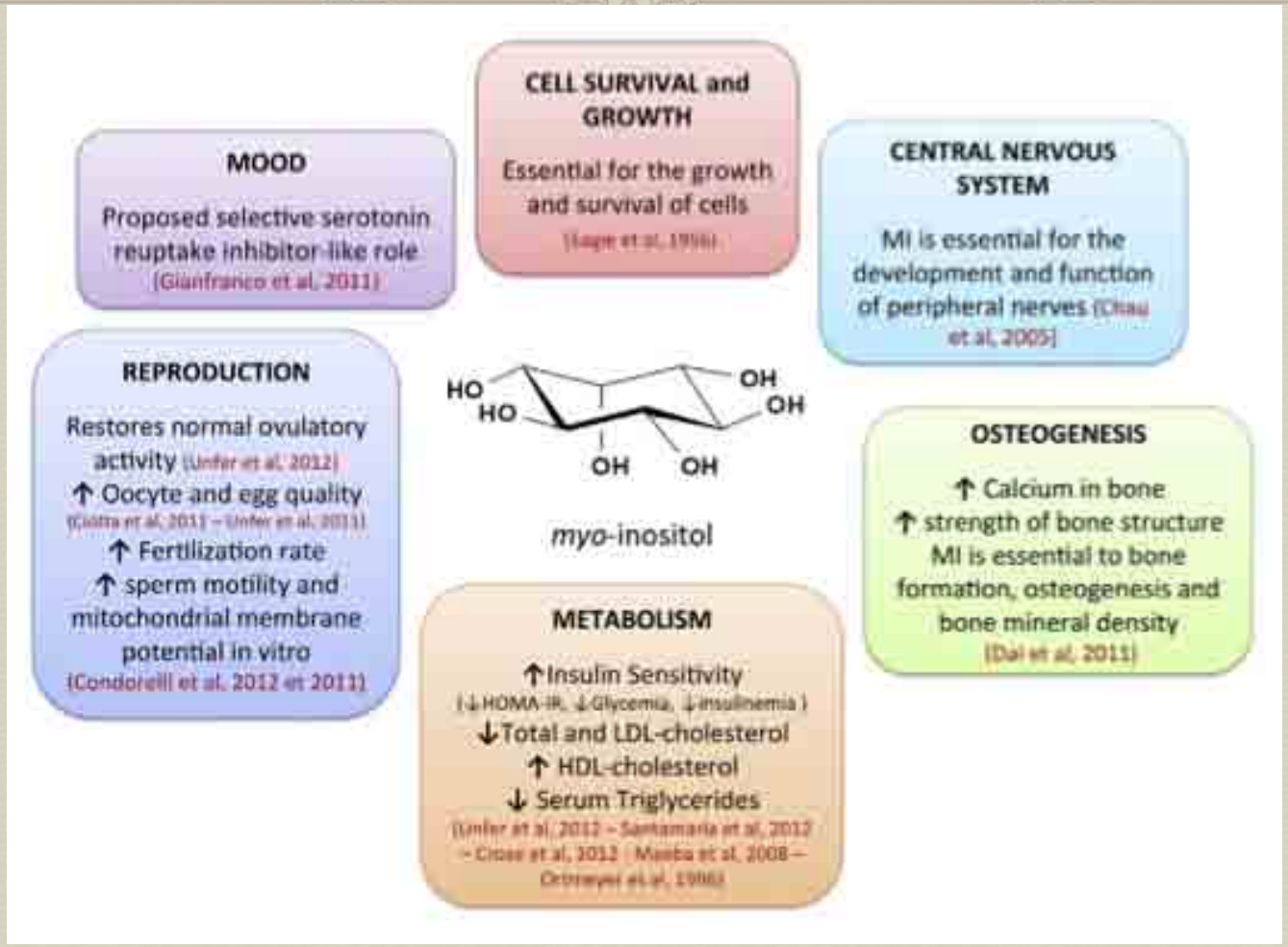
- INS-2 : Pinitolo (3-O-methyl-d-chiro-inositol) beta-1,4- legato alla galattosamina chelata con Mn^{2+} (e non il più comune legame alfa 1,6 presente negli altri inositolo fosfo glicani).


Recettore per l'insulina/IGF-1
SHIP2
PI 3,4P2
PI 3,4,5P3
PI 3P
PTEN
PH
PTB
PY
PI 3-K
Grb2/SOS
SHP2
mTOR
PDK1
PDK2
ras
raf
MEK
MAPK
PHAS
p70s6k
PKCζ/PKCλ
PKB/Akt
FKHR-L1
APX
HNF3
p90rsk
elk1
fos
eIF4
GSK3
BAD
Sintesi proteica
Trasporto del glucosio
Glicogenosintesi
Sopravvivenza cellulare
Trascrizione del gene



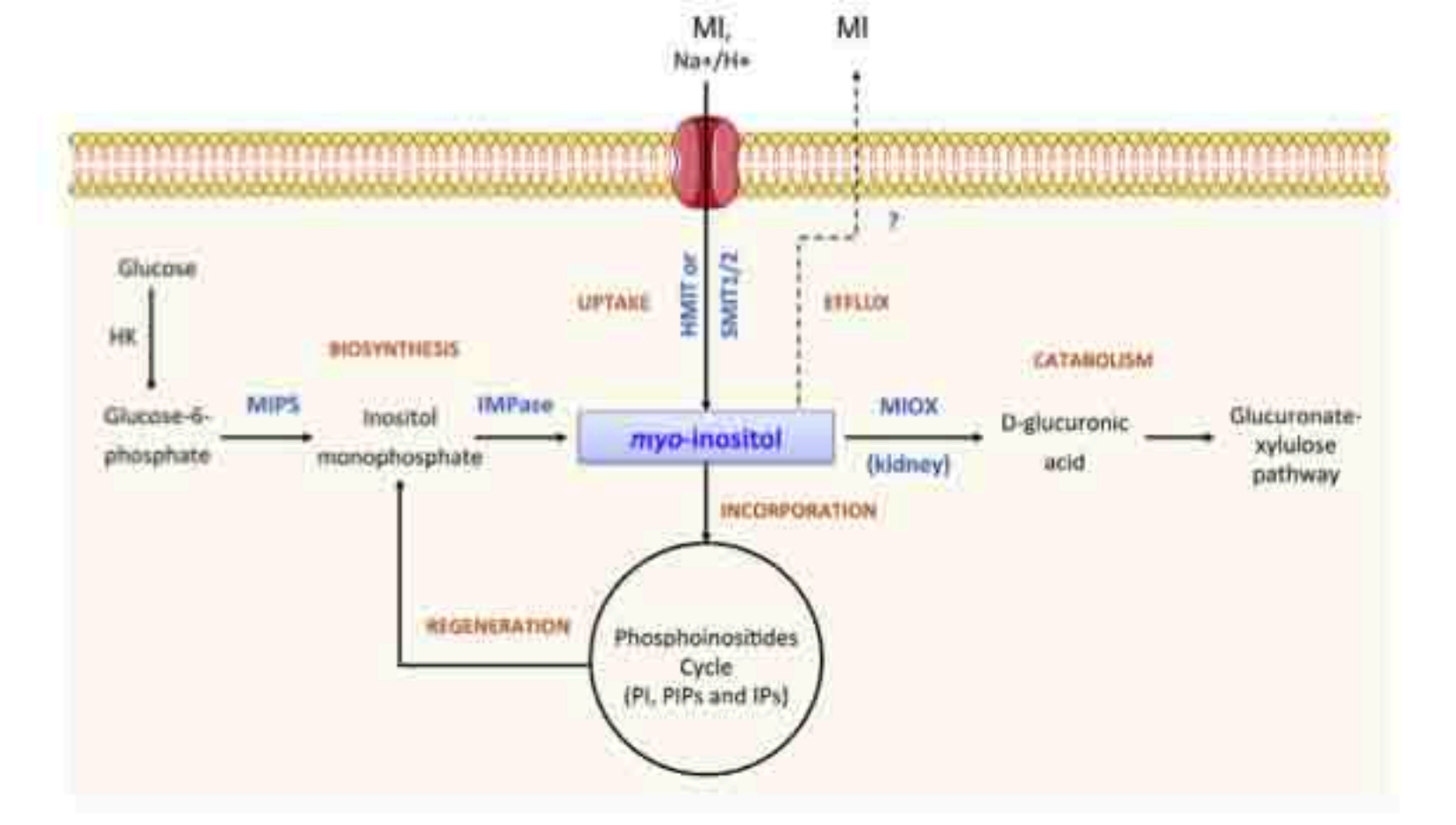
Larner et al, 2010

FUNCTIONS AND BENEFITS OF A MYO-INOSITOL DIET SUPPLEMENT FOR HUMAN HEALTH



Insulino-resistenza e diabete

- Deficit di Mio-inositolo in tessuti insulino-sensibili (rene, nervo sciatico, retina, cristallino).
- Eccessiva escrezione urinaria di mio-inositolo.
- Livelli anormalmente bassi di DCI nei tessuti bersaglio dell'insulina (fegato, muscolo, grasso), nel plasma e nell'urina.



The MI depletion observed under hyperglycemic conditions in insulin sensitive tissues seems to contribute to the development of diabetic microvascular complications, together with the four major and more recognizede pathways :

- ↑ Advanced Glycation End products (AGEs)
- Activation of proyein kinase C (PKC)
- ↑ hexosamine pathway
- ↑ sorbitol pathway

The utility of urinary myo-inositol as a marker of glucose intolerance

Hiroaki Ikezaki a, Norihiro Furusyo a,b,*, Kyoko Okada b, Takeshi Ihara a, Takeo Hayashi a, Eiichi Ogawa b, Mosaburo Kainuma b,Masayuki Murata a,b, Jun Hayashi a,b

abstract

Objective: The most common screening tests for glucose intolerance are fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). Because it reflects the current status of hyperglycemia, urinary myo-inositol (UMI) may be useful. We evaluated UMI as a screening tool for glucose intolerance.

Design and methods: A cross-sectional, community-based population study of 1057 Japanese residents. 173 with an FPG level between 5.5 and 6.9 mmol/L and an HbA1c under 6.5% had an oral glucose tolerance test. We measured UMI level before (fasting UMI) and 2 h after (2 h- UMI) glucose ingestion. D-UMI was defined as the difference between fasting UMI and 2 h- UMI.

Results: D-UMI, 2 h-UMI and HbA1c levels significantly increased as glucose intolerance worsened. D-UMI level was significantly positively correlated with 2 h-UMI level ($r = 0.896$, $p < 0.001$). Using cutoff levels from receiver operating characteristic (ROC) analyses, the sensitivity of D-UMI (82.1%) and 2 h-UMI (79.3%) were higher than that of HbA1c (48.3%). The area under the ROC curve values for D-UMI (0.903) and 2 h-UMI (0.891) were higher than that for HbA1c (0.785).

Conclusions: 2 h-UMI is useful as a non-invasive screening of glucose intolerance.

diabetes research and clinical practice 103 (2014) 88–96

Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials.

Unfer V, Carlomagno G, Dante G, Facchinetti F

Polycystic ovary syndrome (PCOS) affects 5%-10% of women in reproductive age, and it is the most common cause of infertility due to ovarian dysfunction and menstrual irregularity. Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds have been proposed as putative treatments to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia and re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy. Among the insulin-sensitizing compounds, there is myo-inosiol (MYO). Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and consequently fertility, in most patients with PCOS. With the present review, we aim to provide an overview on the clinical outcomes of the MYO use as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

Gynecol Endocrinol. 2012 Jul;28(7):509-15

Reference	Treatment	Inclusion criteria	Results
D'Anna et al., 2013 **From the 1st trimester through the whole pregnancy**	2 g MI þ 200 mg FA twice/day	1) First-degree relatives (mother, father or both) affected by T2D; 2) prepregnancy BMI < 30 kg/m2; 3) fasting plasma glucose <126 mg/ dL and random glycemia <200 mg/ dL; 4) single pregnancy; 5) Caucasian race	**Incidence of gestational diabetes significantly reduced in the MI group compared with the placebo group: 6 vs. 15.3%, respectively (P ¼ 0.04) and reduction of gestational diabetes risk occurrence (odds ratio 0.35). Significantly reduced fasting (p<0.001)and1h-glycemia (p < 0.02) at OGTT in the MI group. A statistically significant reduction of mean fetal weight at delivery in MI group and absence of fetal macrosmia (vs. 7 cases in placebo group). No difference between the groups for the other secondary outcomes studied The incidence of gestational diabetes in mid pregnancy was significantly reduced (p ¼ 0.001) in women who received MI compared to placebo (relative risk 0.127). Women supplemented with MI required less insulin therapy, delivered at a later gestational age, had significantly smaller babies with fewer episodes of neonatal hypoglycaemia.**
Matarrelli et al., 2013 **For the entire pregnancy period**	2 g MI þ 200 mg FA twice/day taken with at least 6 h interval	Consecutive singleton pregnant women with an elevated fasting glucose (glycemia !5.1 mmol/L or 92 mg/dL and 7.0 mmol/L or 1.26 mg/dL) in the 1st or early 2nd trimester	
Santamaria et al. 2012 **12 months**	MI 2 g/day	Postmenopausal women with MetS (at least 3 criteria of the ATP III of the National Cholesterol Education Programme); age between 50 and 60 years old and at least a 12-month period from the last menstruation	**Serum glucose, insulin, HOMA-IR, TG, total and HDL- CST and BP significantly improved with MI compared to placebo. A significant difference from basal values was highlighted only in the MI group (p < 0.0001) for both BMI and WC at 12 months. In the MI group, the number of women without MetS was eight (20%) vs. only one in the control group after 12 months of diet In the group treated with MI, significant improvements in diastolic BP ("11%), HOMA index ("75%), serum TG ("20%) and in HDL cholesterol (þ22%) were observed**
Giordano et **al., 2011 6 months**	MI 2 g/day	Postmenopausal women with MetS (at least 3 criteria of the ATP III of the National Cholesterol Education Programme); Age between 50 and 60 years old and at least a 12-month period from the last menstruation	
Corrado et al., 2011 **8 weeks**	2 g MI þ 200 mg FA twice/ daydInofolic! (MI þ FA)	Gestational diabetes (diagnosed with an OGTT performed between 24 and 28 weeks of gestation)	**Fasting glucose and insulin, and consequently HOMA-IR, decreased in both groups (50% in the MI group vs. 29% in the control group), but the decline in the MI group was significantly greater than that in the control group (P ¼ 0.0001). Adiponectin increased in the MI group while it decreased in the control group (P ¼ 0.009).**
Maeba et al., **2008 2 weeks**	5 g MI/day the 1st week, 10 g MI/day the 2nd week	Male (n ¼ 15) or female (n ¼ 2) hyperlipidemic subjects with (N ¼ 8) or without (N ¼ 9) MetS defined according to Japanese guidelines	**After MI treatment, significant increase in plasmalogen- related parameters, and significant decrease in atherogenic cholesterols including sdLDL were observed. Among the hyperlipidemic subjects treated with MI, subjects with MetS had a significant increase in plasmalogens and a tendency toward reduced sdLDL, hsCRP and blood glucose levels compared to subjects without MetS.**

Pioglitazone treatment in type 2 diabetes mellitus when combined with portion control diet modifies the metabolic syndrome

A.K. Gupta, S.R. Smith, F.L. Greenway, G.A. Bray

Diabetes Obes. Metab. 11 (2009) 330e337.

Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome

K. Esposito, M. Ciotola, D. Carleo, B. Schisano, F. Saccomanno, F.C. Sasso, D. Cozzolino, R. Assaloni, D. Merante, A. Ceriello, D. Giugliano

Diabetes Care 29 (2006) 1071e1076.

MI is more effective than rosiglitazone in reducing serum triglycerides but less effective than pioglitazone (Pioglitazone ("50%) > myo-inositol ("34%) > Rosiglitazone ("20%))

Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: a post-hoc analysis of the BIGPRO1 trial

Fontbonne, I. Diouf, M. Baccara-Dinet, E. Eschwege, M.-A. Charles

Diabetes Metab. 35 (2009) 385e391.

no change in triglycerides was noted, but only a slight improvement of HDL cholesterol (+2.4%)

Effects of D-chiroinositol added to a meal on plasma glucose and insulin in hyperinsulinemic rhesus monkeys,

H.K. Ortmeyer, J. Larner, B.C. Hansen

Obes. Res. 3 (Suppl. 4) (1995) 605Se608S.

Insulin-like effect of pinitol

S.H. Bates, R.B. Jones, C.J. Bailey

Br. J. Pharmacol. 130 (2000) 1944e1948.

Pinitol from soybeans reduces postprandial blood glucose in patients with type 2 diabetes mellitus

M.-J. Kang, J.-I. Kim, S.-Y. Yoon, J.C. Kim, I.-J. Cha

J. Med. Food 9 (2006) 182e186.,

Effects of pinitol isolated from soybeans on glycaemic control and cardiovascular risk factors in Korean patients with type II diabetes mellitus: a randomized controlled study

J.-I. Kim, J.C. Kim, M.-J. Kang, M.-S. Lee, J.-J. Kim, I.-J. Chatudy

Eur. J. Clin. Nutr. 59 (2005) 456e458.

Herbal constituent sequoyitol improves hyperglycemia and glucose intol- erance by targeting hepatocytes, adipocytes, and b-cells,

H. Shen, M. Shao, K.W. Cho, S. Wang, Z. Chen, L. Sheng, T. Wang, Y. Liu, L. Rui,

Am. J. Physiol. Endocrinol. Metab. 302 (2012) E932eE940.

both subcutaneous and oral administrations of sequoyitol (80 mg/kg per day) for 8-10 weeks improved hyperglycemia, glucose intolerance and enhanced insulin signaling in liver of ob/ob insulin resistant mice

D-pinitol and myo-inositol stimulate translocation of glucose transporter 4 in skeletal muscle of C57BL/ 6 mice

N.T. Dang, R. Mukai, K.-I. Yoshida, H. Ashida, Biosci.
Biotechnol. Biochem. 74 (2010) 1062e1067.

This effect was associated with an improvement in peripheral insulin sensitivity established in vivo during an insulin tolerance test and further confirmed by the observation of an enhanced GLUT-4 translocation to the plasma membrane in response to hyperglycemia in the skeletal muscle .

CONCLUSIONI

1. Le proprietà insulino-mimetiche della supplementazione dietetica è ritenuta essere principalmente correlata alla produzione degli inositolo-glicani contenenti sia MI che DCI e che funzionano da secondi messaggeri.
2. Ulteriori studi sono necessari per chiarire l'esatto meccanismo di azione del MI e di confermare o meno la IPGs ipotesi.
3. Studi clinici di controllo randomizzati condotti sulla supplementazione con MI hanno dato risultati positivi nel contrastare l'insulino resistenza e nel ridurre i fattori di rischio CV in donne con PCOS, in donne con diabete gestazionale e donne in post menopausa e con sindrome metabolica.
4. Tuttavia, studi ulteriori, più ampi, in doppio cieco ed includenti anche popolazioni di origine non caucasica e soprattutto uomini sono necessari per :
    1. Confermare i risultati ottenuti su donne con DMT2, PCOS o in post menopausa e sindrome metabolica.
    2. Valutare la possibile applicazione per una popolazione più generalizzata di soggetti che già presentano una insulino resistenza o a rischio di svilupparne una per una predisposizione genetica.

GRAZIE PER L'ATTENZIONE