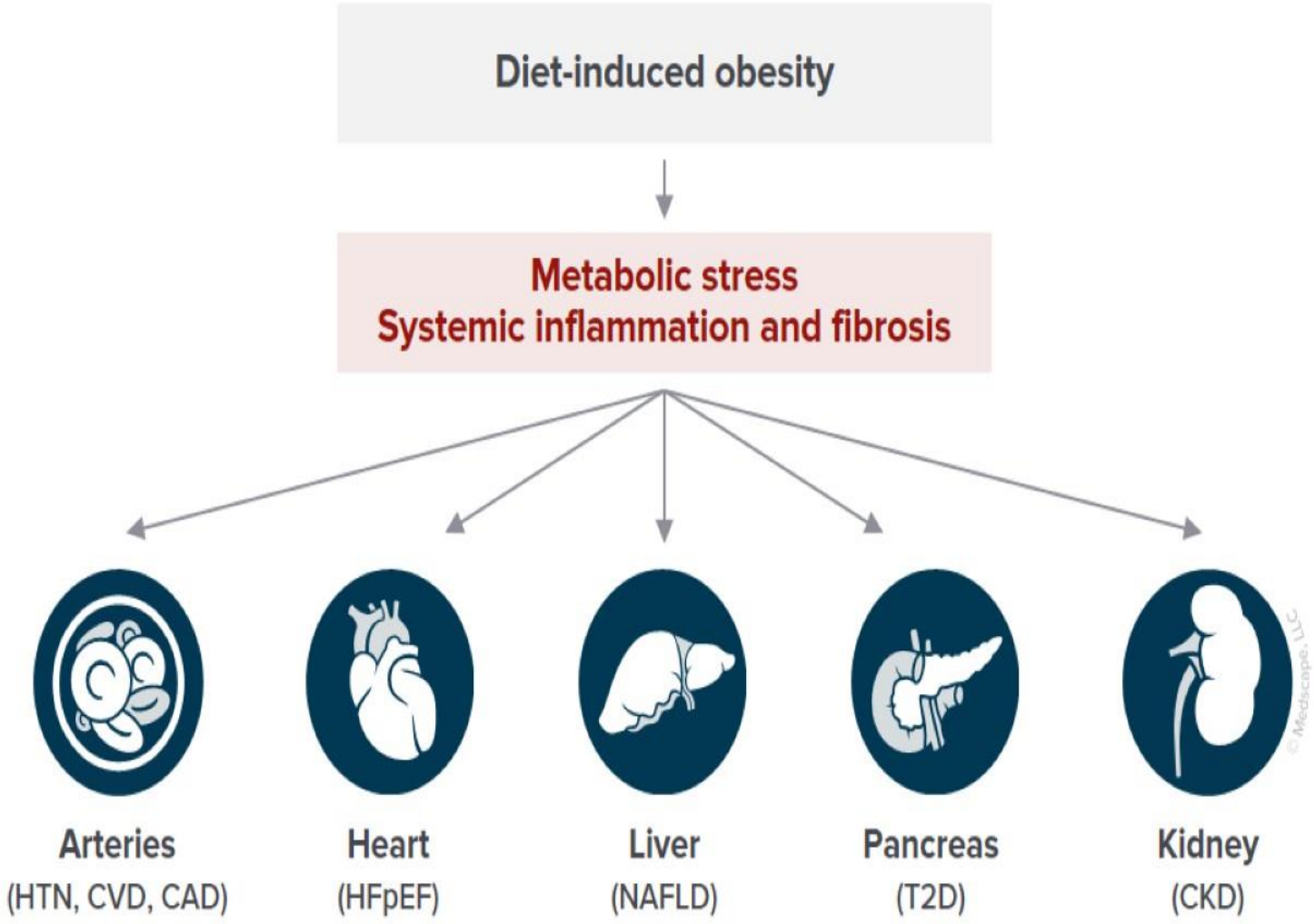
UNIVERSITY ABOUBEKR BELKAID	LABORATORY OF RESEARCH ON DIABETES مخبر بحث سكري « LAREDIAB » Code ATRSS/DGRST N° W0417700 FACULTY OF MEDICINE BENAOUDA BENZERDJEB https://larediab.univ-tlemcen.dz Mobile : 0770 218 100 / E-mail: ali.lounici@univ-tlemcen.dz AMIWIT	ACADEMIC HOSPITAL TIDJANI DAMERDJI

INSULIN RESISTANCE AND MULTI-SYSTEM DISORDER

2ND SÉMINARY OF LAREDIAB
8TH CONGRESS OF AMIWIT

WEDNESDAY 9 ET THURSDAY 10 JUNE 2021
FACULTY OF MEDICINE BENAOUDA BENZERDJEB

NAFLD Is Part of a Multi-System Disorder



Friedman SL et al. *Nat Med*. 2018;24:908-922.

Type 2 Diabetes & Insulin Resistance

- Diabetes risk

- T2D heterogeneous condition characterized by varying degrees of reduced β-cell function and higher levels of insulin resistance (IR).
- IR is generally believed to be the first abnormality leading to glucose intolerance.
- Lorenzo et al., found that MetS without pre-diabetes carries an approximate 5-fold increase in diabetes risk. For patients with IFG or impaired glucose tolerance (IGT), the diabetes risk is 5- to 7-fold higher for than normoglycemia. However, when pre-diabetes combines with MetS, the risk is increased even more (Lorenzo et al. 2007: *Diabetes Care* 30: 8–13)

Type 2 Diabetes & Insulin Resistance

Targeting patients with IR at diagnosis of diabetes:

- The approach of precision medicine in diabetes is targeting patients with insulin-resistance at diagnosis of diabetes.
- The recent Scandinavian classification, published in 2018, proposed 5 clusters of diabetes mellitus in adults.
- They demonstrated that diabetic classified as cluster 3 (most resistant to insulin), labelled as “Severe Insulin-Resistance Diabetes” had significantly higher risk of developing diabetic kidney disease than individuals in cluster 4, labelled as “Mild Obesity-Related Diabetes” or cluster 5, labelled as “Mild Age-Related Diabetes”

[Ahlqvist et al. 2018 : *Diabetes Care* 6: 520].

Type 2 Diabetes & Insulin Resistance

Metabolic memory = legacy effects

Evidence suggests that early treatment is crucial for prevention of life-shortening complications because target tissues seem to remember poor metabolic control decades later.

This legacy effects (also called metabolic memory)have been demonstrated in two post trials long-term observational follow-up

[Chalmers and Cooper 2008 : *New England Journal of Medicine* 359: 1618–20]

The UK Prospective Diabetes Study (UKPDS)trial revealed that the early glycemic control in patients with type 2 diabetes has durable effects on microvascular and macrovascular events 10 years after the trial ended

[Holman et al. 2008 : *New England Journal of Medicine* 359: 1577–89]

The Diabetes Control and Complications Trial(DCCT), showed that intensive diabetes therapy has long-term beneficial effects on the incidence of cardiovascular disease in type 1 diabetes that persist for up to 30 years

[Gubitosi-Klug et al. 2016: *Diabetes Care* 39: 686–93]

In the recent large cohort Diabetes & Aging study of patients with newly diagnosed T2D and at least10 years of survival after diagnosis, the authors found that diabetes control during the first year after diagnosis was strongly associated with future risk for diabetic complications and mortality, even after adjusting for glycemic control after the first year. These findings underscore the urgency of early diagnosis of diabetes with immediate and intensive treatment for newly diagnosed patients to avoid irremediable long-term risk for diabetic complications and mortality

[Laiteerapong et al. 2019: *Diabetes Care* 42: 416–26]

Type 2 Diabetes & Insulin Resistance

Diabetes Prevention

Evidence of the effectiveness of diet and exercise in the primary prevention of T2D makes the identification of people at risk of developing this pathology essential.

- Several major randomized controlled trials demonstrate that changes in lifestyle is highly effective in preventing type 2 diabetes.
- Diabetes Prevention Program (DPP)

  [Knowler et al. 2002: *The New England journal of medicine* 346(6): 393–403]
- Finnish Diabetes Prevention Study (DPS)

  [FDPS 2001 : *New England Journal of Medicine* 344(18): 1343–50]
- Da Qing Diabetes Prevention Study (Da Qing study)

  [Pan et al. 1997: *Diabetes Care* 20: 537–44]

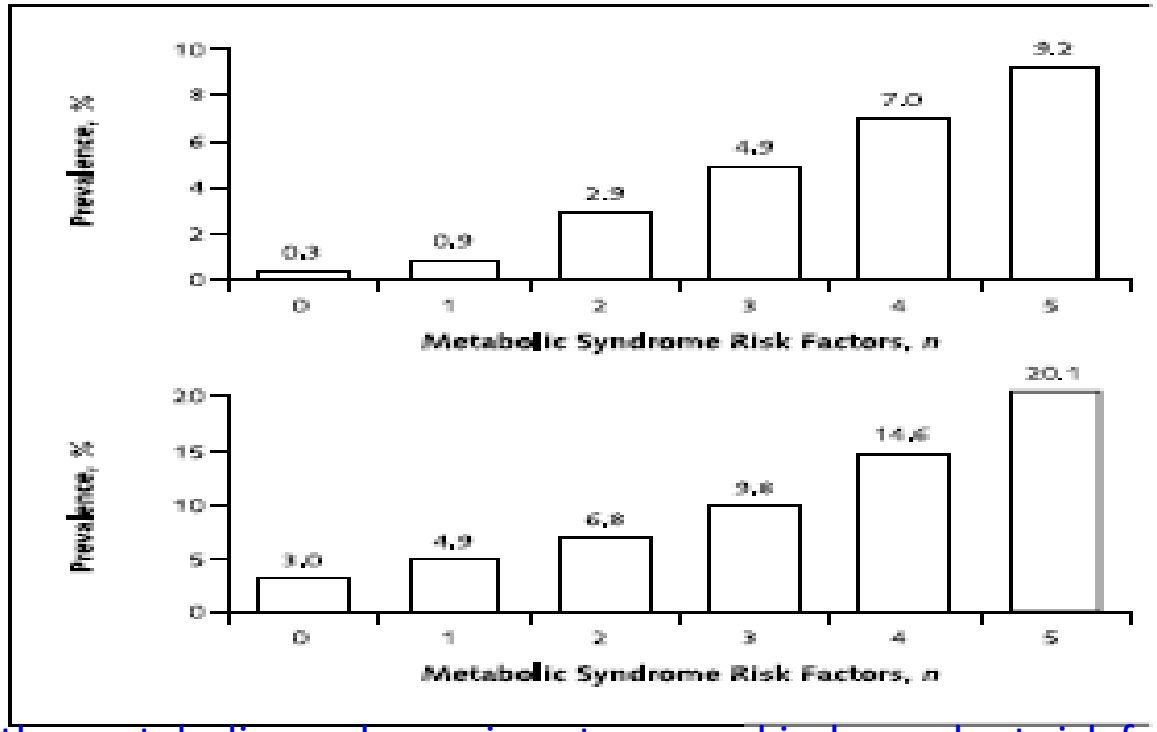
Hypertension & Insulin Resistance

- Abundant clinical and epidemiologic evidences demonstrate a close linkage between insulin resistance and hypertension. The coexistence of insulin resistance and hypertension results in a substantial increase in the risk of developing cardiovascular disease and type II diabetes
    - [Lastra et al. 2010: *Nature Reviews Cardiology* 7(10): 577–84].
- Hypertension and type 2 diabetes mellitus (T2DM) are powerful risk factors for cardiovascular disease (CVD) and chronic kidney disease (CKD), both of which are leading causes of morbidity and mortality worldwide. Research into the pathophysiology of CVD and CKD risk factors has identified salt sensitivity and insulin resistance as key elements underlying the relationship between hypertension and T2DM .
    - [Lastra et al. 2010: *Nature Reviews Cardiology* 7(10): 577–84].

- The *renin-angiotensin aldosterone system* (RAAS) contributes to the underlying pathophysiology of insulin resistance. Drugs that blockade of the RAAS has been shown to improve insulin sensitivity, produce a significant decline of albuminuria, induce a drop of the pathological glomerular hyperfiltration, and reduce the incidence of new-onset diabetes **[Underwood and Adler 2013: *Current hypertension reports* 15: 59–70]**

KIDNEY & INSULINO-RESISTANCE

Figure 2. **Prevalence of chronic kidney disease (*top*) and microalbuminuria (*bottom*) by number of the metabolic syndrome components.**



Data suggest that the metabolic syndrome is a strong and independent risk factor for chronic kidney disease and microalbuminuria. In addition**, there is a graded relationship between the number of metabolic syndrome components and risk for chronic kidney disease or microalbuminuria** [Chen et al. 2004: *Annals of Internal Medicine* 140(3)].

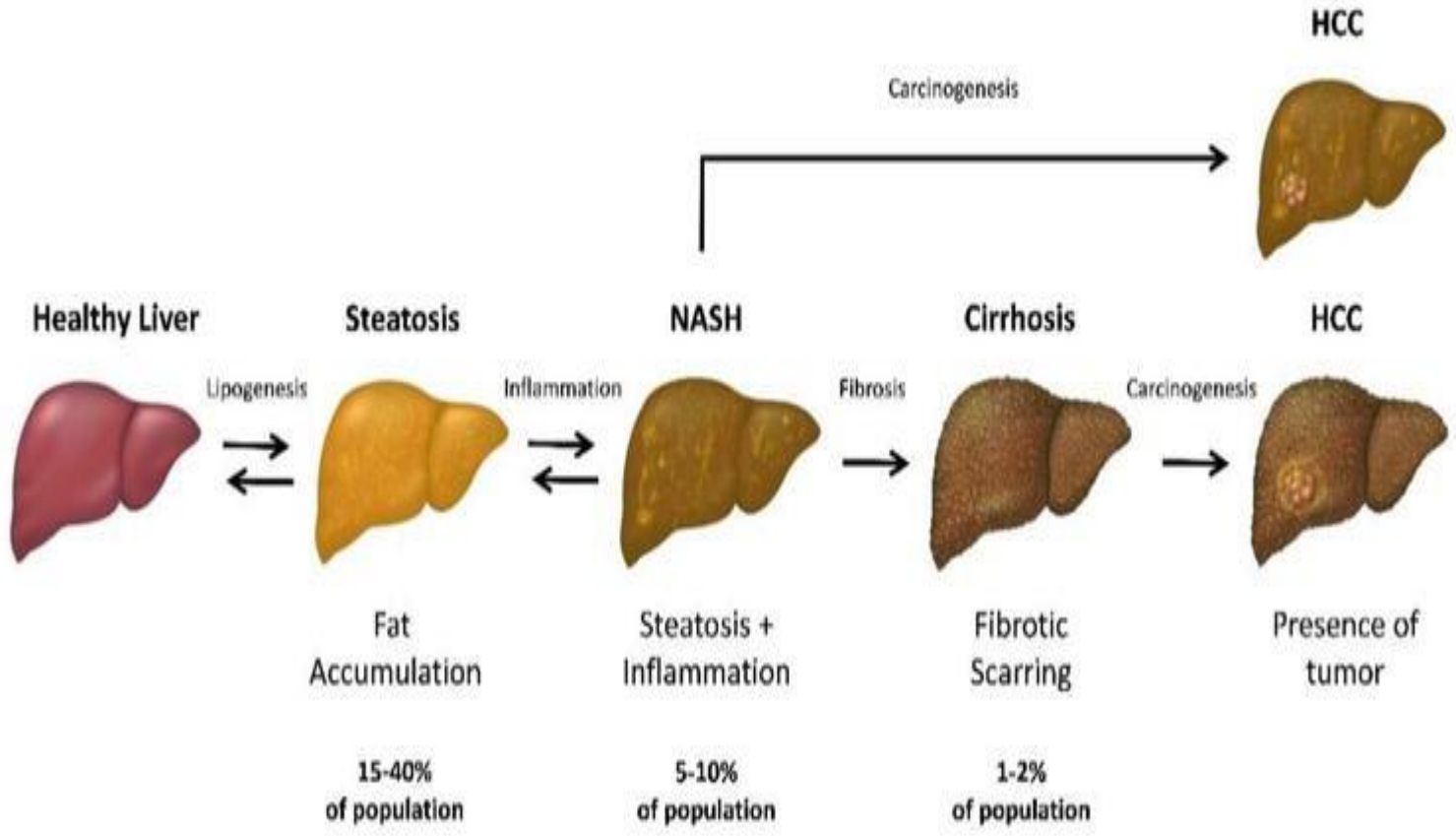
These findings warrant intervention studies to prevent and treat the metabolic syndrome in order to reduce the risk for chronic kidney disease and microalbuminuria

KIDNEY & INSULINO-RESISTANCE

- The Scandinavian study demonstrated that diabetic with “severe insulin-resistance” had significantly higher risk of developing diabetic kidney disease than individuals “without insulin-resistance”

[Ahlqvist 2018 : *Diabetes Care* 6: 520]

Liver disease and Insulin resistance



Clin Liver Dis. 2018; 22: 11–21

Liver disease and Insulin resistance

- Non alcoholic steatohepatitis (NASH) is a severe inflammatory form of non alcoholic fatty liver disease (NAFLD) that is characterized by the accumulation of fat (steatosis), hepatocyte damage, and inflammation. It is associated with disease progression, development of fibrosis, cirrhosis, need for liver transplant and an increased risk of hepatocellular carcinoma **(Lindenmeyer and McCullough 2018).**
- Data support the novel paradigm of nonalcoholic fatty liver disease as a strong determinant for the development of the metabolic syndrome and insulin resistance represents its pathophysiological hallmark **(Lonardo et al. 2015).**
- The systematic review and meta-analysis of 4428 patients in 13 studies found that, with and without adjustments for potential confounding factors, biopsy-confirmed fibrosis stage was associated with all-cause mortality, liver-related mortality, and morbidity in patients with NAFLD **(Taylor et al. 2020).**
- There is clearly an increased risk of developing hepatocellular carcinoma (HCC) among patients with NASH cirrhosis. A review of several recent studies assessing the outcome of patients with NASH cirrhosis demonstrates that 7% will progress to HCC during 6.5 years of follow-up. Data now suggest that HCC can also occur in NASH patients without advanced fibrosis **(Torres, Williams, and Harrison 2012)**
- Early identification and targeted treatment of patients with NASH are needed to improve patient outcomes, including directing patients toward intensive lifestyle modification to promote weight loss and referral for bariatric surgery as indicated for management of obesity and metabolic disease **(Sheka et al. 2020).**
- Ultimate goal is to achieve and sustain weight loss of 7% to 10% of bodyweight, as this has been shown to improve the majority of histopathological features of NASH **(Promrat et al. 2010)**

Cardiovascular and disease Insulin resistance

- A large prospective studies have shown that hyperinsulinemia is a predictor of coronary artery disease (CAD). The greatest association of hyperinsulinemia with CAD has been found in Finland in a population with a very high frequency of CAD **[Pyörälä et al. 1998: *Circulation* 98(5): 398–404]**
- Results of a prospective investigation of 2103 men from Quebec clearly showed that high fasting insulin concentrations are an independent predictor of CAD **[Després 1996: *New England Journal of Medicine* 334(15): 952–58]**
- **Several studies have shown a relationship between insulin levels/resistance and :**
- Carotid wall atherosclerotic lesions **[Ishizaka et al. 2003: *Arteriosclerosis, Thrombosis, and Vascular Biology* 23(2): 295–301] and**
- Angina **[Rewers 2004: *Diabetes Care* 27: 781–87]**

Cognitive decline and Insulin resistance

- Insulin resistance predicts cognitive decline, specifically in the memory domain, in persons with prediabetes [Willmann et al. 2020: *BMJ Open Diabetes Research and Care* 8: 1741]
- Multiple studies demonstrate a strong connection between MetS and the increased risk of AD [Kim and Feldman 2015: *Experimental & molecular medicine* 47(3): e149]
- Investigators are now accumulating evidence to support the assertion that prevention and treatment of insulin resistance (IR) may help to lessen cognitive decline later in life (Ayubi and Safiri 2017). A large, 11-year, longitudinal study from Finland [Ayubi 2017: Diabetes Care 2017;40:751-75], as well as several smaller longitudinal trials, link insulin resistance to cognitive decline, supporting the findings of a major National, Heart, Lung and Blood Institute trial [Young 2006: *Diabetes Care* 29(12): 2688–93]
- Investigators recommend that clinicians consider these findings in encouraging patients to adopt lifestyle changes that may prevent or slow cognitive decline.

INSULINO-RESISTANCE & INFLAMMATORY DISEASES

INSULINO-RESISTANCE & INFLAMMATORY DISEASES

Haroon, M., High prevalence of metabolic syndrome and of insulin resistance in psoriatic arthritis is associated with the severity of underlying disease. ***J. Rheumatol.*** **41, 1357–1365 (2014).**

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Pernicova, I. *et al.* Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. *Lancet Diabetes Endocrinol.* **8**, 278–291 (2020).

RESEARCH ARTICLE

Is insulin resistance the cause of fibromyalgia? A preliminary report

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OPEN ACCESS

Citation: Pappolla MA, Manchikanti L, Andersen CR, Greig NH, Ahmed F, Fang X, et al. (2019) Is insulin resistance the cause of fibromyalgia? A preliminary report. PLoS ONE 14(5): e0216079. https://doi.org/10.1371/journal.pone.0216079

Abstract

Fibromyalgia (FM) is s with poorly understood neurobic enormous proportion of healthcare costs. I known and thus, there is no disease modifyi at most (if not all) patients with FM bel from a control group by their glycated her nsulin resistance (IR). This was demon ge stratification correction into a linear regression model. This strategy showed highly significant differences between FM patients and control subjects ($p < 0.0001$ and $p = 0.0002$, for two separate control populations, respectively). A subgroup of patients meeting criteria for pre-diabetes or diabetes (patients with HbA1c values of 5.7% or greater) who had undergone treatment with metformin showed dramatic improvements of their widespread myofascial pain, as shown by their scores using a pre and post-treatment numerical pain rating scale (NPRS) for evaluation. Although preliminary, these findings suggest a pathogenetic relationship between FM and IR, which may lead to a radical paradigm shift in the management of this disorder.

Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial

Ida Pernicova, Stephen Kelly, Sharon Ajodha, Anju Sahdev, Jonathan P Bestwick, Plamena Gabrovska, Olufunso Akanle, Ramzi Ajjan, Blerina Kola, Marietta Stadler, William Fraser, Miriam Christ-Crain, Ashley B Grossman, Costantino Pitzalis, Márta Korbonits

www.thelancet.com/diabetes-endocrinology Published online February 25, 2020 https://doi.org/10.1016/S2213-8587(20)30021-8

Metformin: the white knight fighting corticosteroid side-effects

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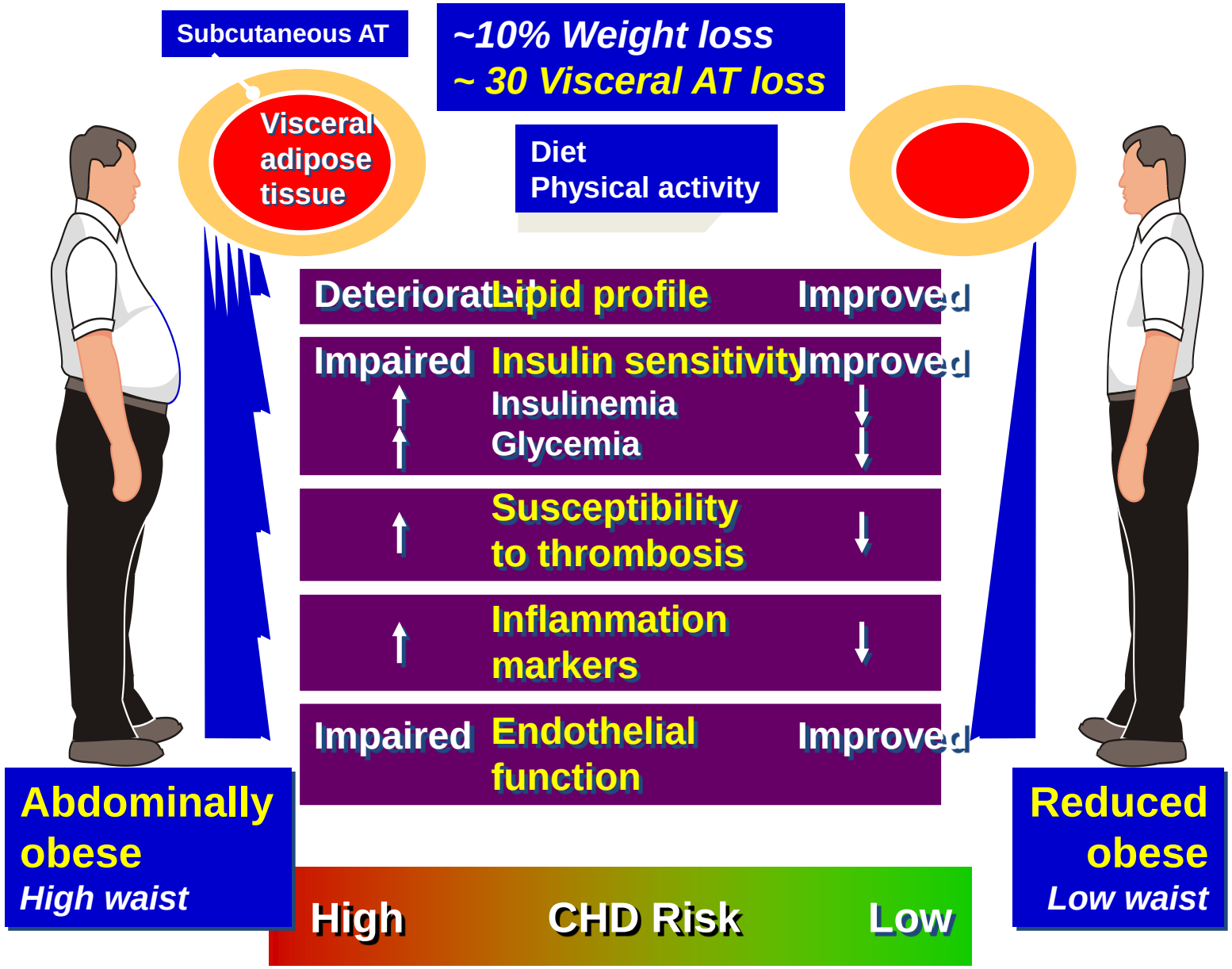
Lancet Diabetes Endocrinol 2020

Published Online
February 25, 2020
https://doi.org/10.1016/
S2213-8587(20)30040-1

See Online/Articles
https://doi.org/10.1016/
S2213-8587(20)30021-8

IMPLICATIONS



Adapted from Després et al. BMJ (2001) 322:716-720

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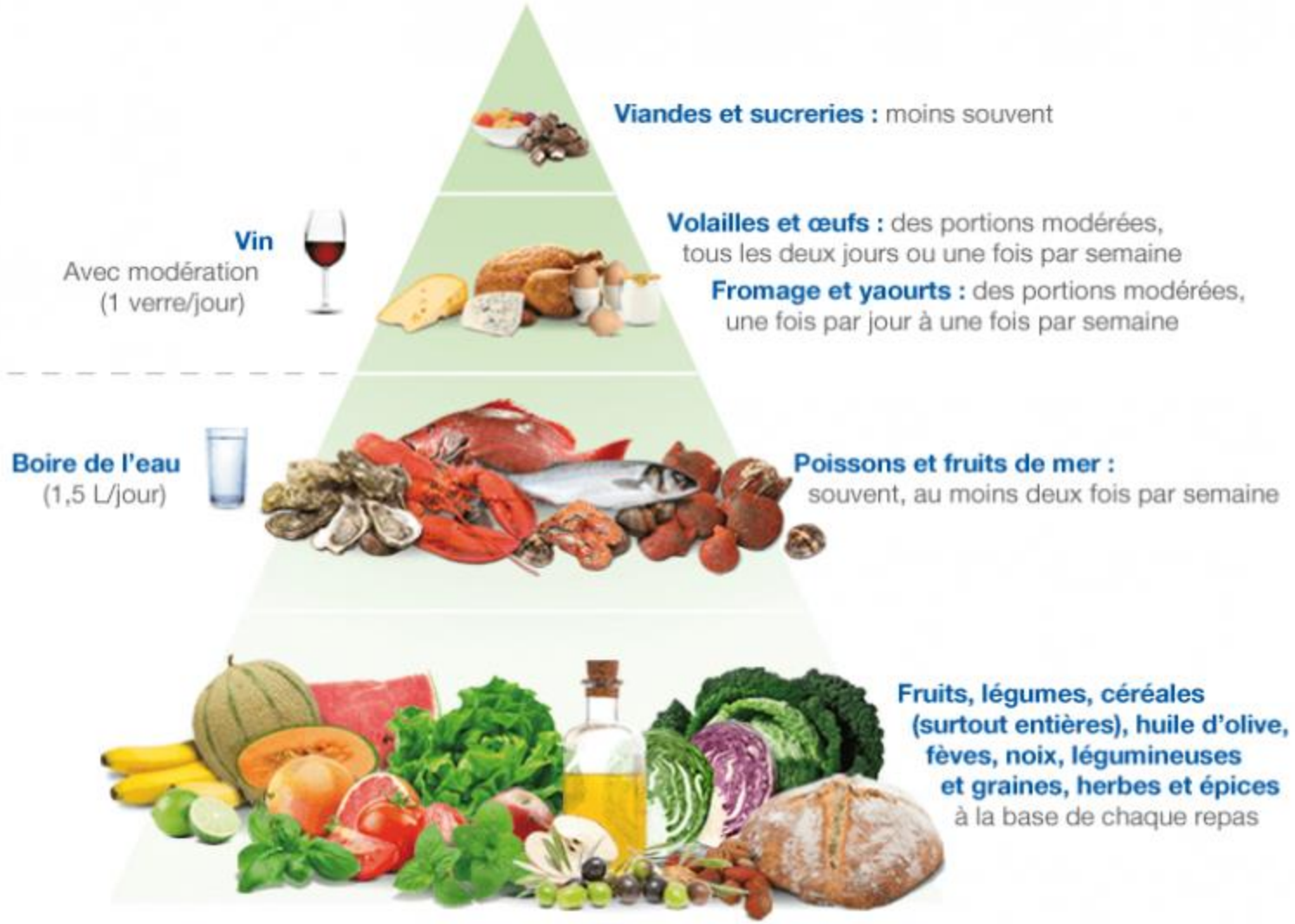

La pyramide du régime crétois. (d'après Willett, 1995)

Published in final edited form as:
Curr Hypertens Rep. 2011 February ; 13(1): 67–73. doi:10.1007/s11906-010-0168-5.

The DASH Diet and Insulin Sensitivity

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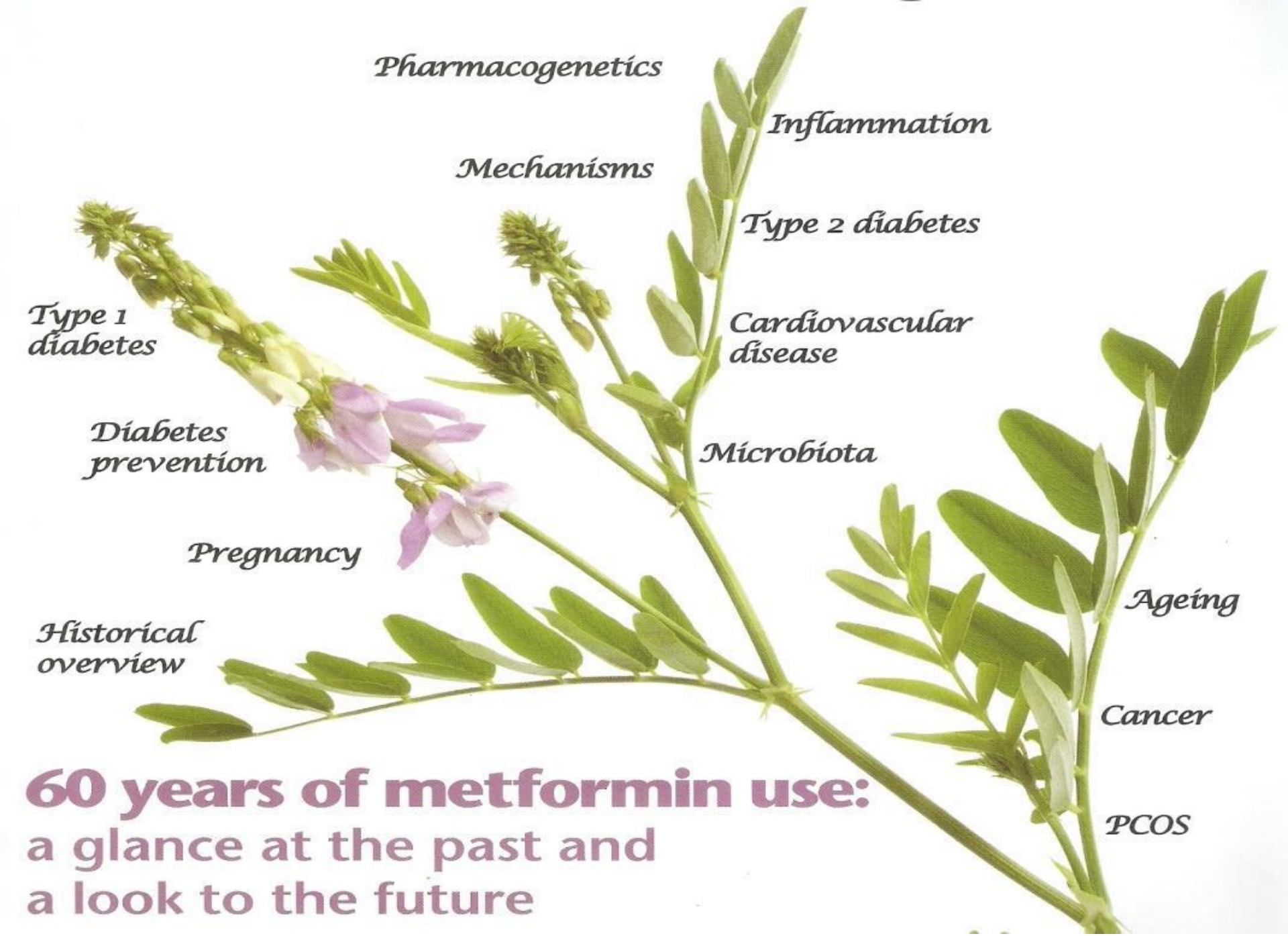
Abstract

Lifestyle modifications, including adoption of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, weight loss in individuals who are overweight or obese, and physical

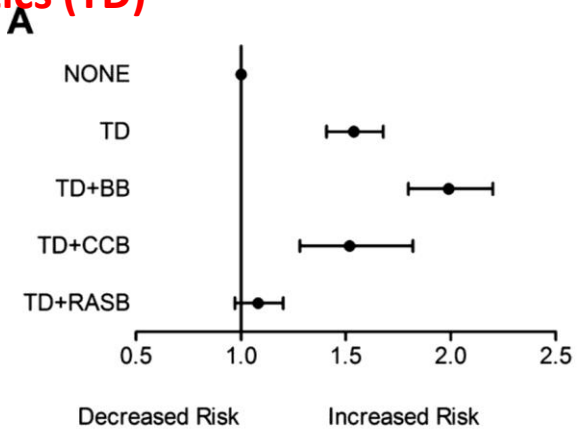


60 years of metformin use: a glance at the past and a look to the future

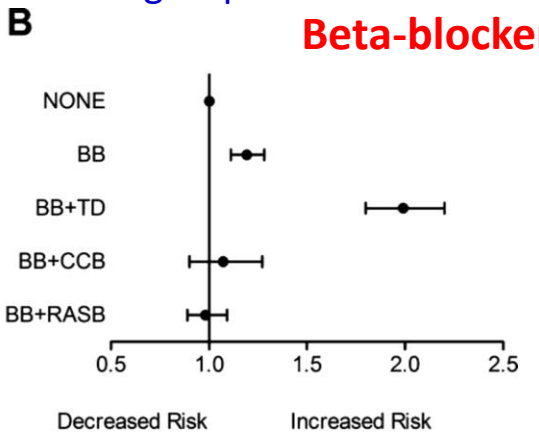
Diabetogenic potential of combination therapy should be considered when prescribing antihypertensive therapy

Adjusted odds ratio and 95% confidence interval for risk of diabetes among members in the Kaiser Permanente Northwest database who were prescribed alone or in combination. Members exposed to none of the drug classes constitute the reference group.

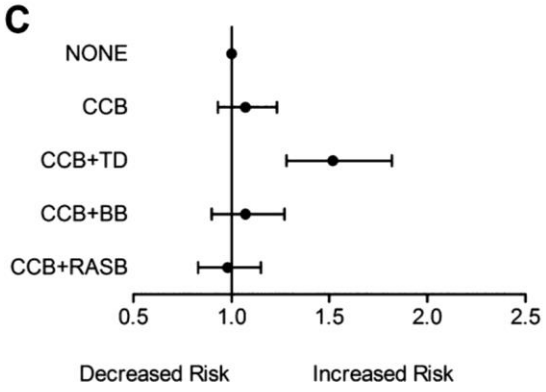
Thiazide diuretics (TD)



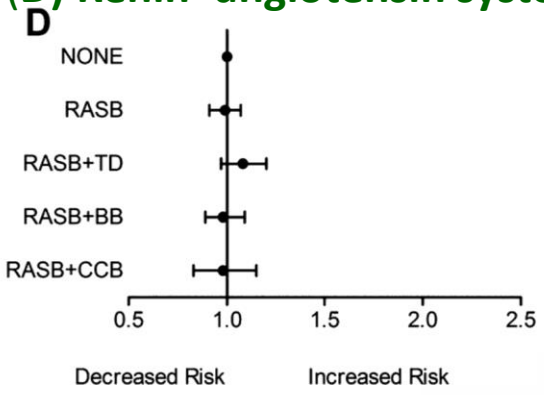
Beta-blockers (BB)



Calcium channel blockers (CCB)



(D) Renin–angiotensin system blockers (RASB



Cooper-DeHoff R et al. J Am Heart Assoc. 2013;2:e000125 doi: 10.1161/JAHA.113.000125

American Heart Association | American Stroke Association

LIPIDS DISORDERS = TARGET NON-HDL

- **QUANTITATIVE DISORDERS**
- **(↑TG , ↓HDL) LDL = 0**
- **QUALITATIVE DISORDERS**
  - **↑ Large size VLDL production (VLDL 1)**
  - **LDL enrichment in TG (↑ small and dense LDL)**
  - **HDL enrichment in TG**
  - Glycation of apolipoproteins
  - Oxidation of Lipoproteins (LDL ++)

= ATHEROGENES

THANKS

FOR YOUR ATTENTION