Metabolic syndrome and rheumatoid arthritis

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Disclosures

- Speaker: Astra Zeneca, Abbott Nutrición, Novartis, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer
- Clinical Investigation: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk, Novartis Oncology

Agenda

- Definition of metabolic syndrome (MS)
- Pathophysiology
- Association of MS and RA
- What are the consequences?
- How do we assess cardiovascular risk in patients with RA?
- What to do?

Clinical case

- 65 years old female patient, with RA treated with hydroxychloroquine
- Hypothyroidism diagnosed in 2016, treated with levothyroxine 50 ug per day
- Weight 69 kg, height 160 cm. BMI 26.95 kg/m2. BP 130/80 mm Hg
- Initial assessment (nov 2016), taking lovastatine 20 mg per day
  - Hba1c 6.6%
  - Total cholesterol 182 mg/dl
  - HDL 49 mg/dl
  - Triglycerides 150 mg/dl
  - LDL 103 mg/dl

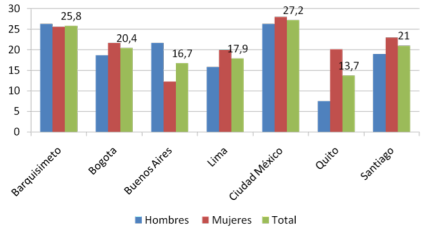
Questions

- Does the patient have metabolic syndrome?
  1. Yes
  2. No
  3. I am not sure

What is this patient's cardiovascular risk?

- Low
- Intermediate
- High
- Very high

Estudio CARMELA



Schargrodski H. Am J Med. 2008;121:58-65.

2005 Revised ATP III Clinical Screening Criteria to Identify Metabolic Syndrome (AHA and NHLBI)

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical cutpoints
Elevated waist circumference	≥102 cm in men ≥88 cm in women
Elevated triglycerides	≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides
Reduced HDL-cholesterol	<40 mg/dl (0.9 mmol/l) in men <50 mg/dl (1.1 mmol/l) in women Or on drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dl or on drug treatment for elevated glucose

Diagnosis of The Metabolic Syndrome

IDF CRITERIA (2005)

- Central obesity (defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups)

- Plus any two of the following four factors
  - TG ≥150 mg/dl (1.7 mmol/l), or specific treatment for this lipid abnormality
  - HDL <40 mg/l (1.03 mmol/l) in males and <50 mg/l (1.29 mmol/l) in females, or specific treatment for this lipid abnormality
  - Systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension
  - Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l), or previously diagnosed type 2 diabetes. If above 5.6 mmol/l or 100 mg/dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome

Diagnosis of The Metabolic Syndrome

IDF CRITERIA (2005)

Ethnic-specific cut-points for waist circumference

Country/Ethnic group		Waist circumference (as measure of central obesity)
Europids	Male	≥94 cm
	Female	≥80 cm
South Asians	Male	≥90 cm
	Female	≥80 cm
Chinese	Male	≥90 cm
	Female	≥80 cm
Japanese	Male	≥85 cm
	Female	≥90 cm

Diagnosis of The Metabolic Syndrome

IDF CRITERIA (2005)

Ethnic-specific cut-points for waist circumference

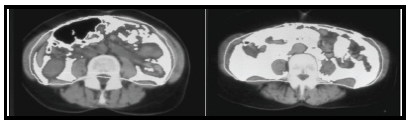
Country/Ethnic group	Waist circumference (as measure of central obesity)
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available

Definition

Definitions	WHO	NCEP-ATP III	IDF	EGIR	AACE	AHA/NHLBI	ATP III	JS 2009
Number of Criteria	Two or more of:	Three or more of:	Two or more of	Two or more of:	Obesity and two or more of:	Three or more of:	Three or more of:	Three or more of:
Obesity	BMI > 30 and/or WHR > 0.9 (men), WHR > 0.85 (women)	WC ≥ 102 cm (men), WC ≥ 88 cm (women	WC ≥ 94 cm men, WC ≥ 80 cm women	WC ≥ 94 cm (men, WC ≥80 cm (women)	WC ≥ 102 cm (men), WC ≥ 88 cm (women	BMI ≥ 30 kg/m2	WC ≥ 102 cm (men), WC ≥ 88 cm (women	Population- and country-specific definitions
Blood pressure mmhg	≥ 140/90	≥ 130/85 or treatment	≥130/≥85 or treatment	≥ 140/90	≥ 130/85 or treatment	≥130/85 mmHg or previous hypertension diagnosis	≥ 130/85 or treatment	≥ 130/85 or treatment
Dyslipidmia:								
HDL-C	≥ 35 mg/dL (0.9 mmol/L) in men or ≥ 39 mg/dL (≥ 1.0 mmol/L) in women	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/ dL (1.29 mmol/ L) in women, or treatment	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women, or treatment	≥ 39 mg/ dL (1.0 mmol/L) or treatment	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/ dL (1.29 mmol/ L) in women, or treatment	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/ dL (1.29 mmol/L) in women	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/ L) in women	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/ dL (1.29 mmol/ L) in women, or treatment
Triglycerides	≥178 mg/dL(2.0 mmol/L) or treatment	≥150 mg/dL (1.7 mmol/L) or treatment	≥150 mg/dL (1.7 mmol/L) or treatment	≥150 mg/ dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or treatment	≥150 mg/dL (1.7 mmol/L) or treatment	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or treatment
Glucose Intolerance or Fasting Plasma Glucose	≥110 mg/dL (6.1 mmol/l), DM, IGT, IR	≥100 mg/dL (5.6 mmol/L) or T2D	≥100 mg/dL (5.6 mmol/L) or T2D	≥110 mg/ dL (6.1 mmol/L)	≥110 mg/dL (6.1 mmol/l), or treatment	≥100 mg/dL (5.6 mmol/L) or T2D	≥110 mg/dL (6.1 mmol/L)	≥100 mg/dL (5.6 mmol/L) or T2D

Hallajzadeh J. PLos One. 2017;12:e0107361

Some Patients have Predominant Visceral Fat

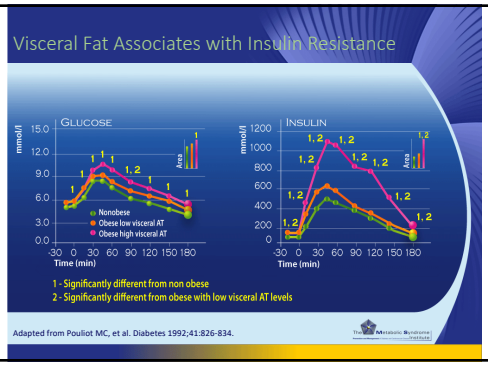


Moderate Visceral Obesity with little Abdominal Subcutaneous Fat

Severe Visceral Obesity with little Abdominal Subcutaneous Fat

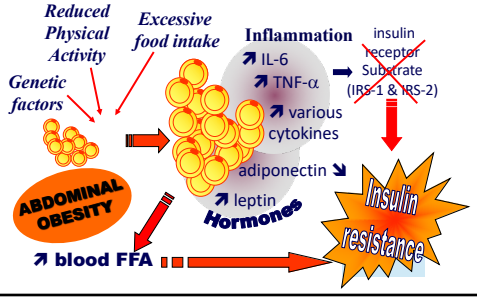
Fujimoto, et al. Obes Res. 1994;2:364-371.

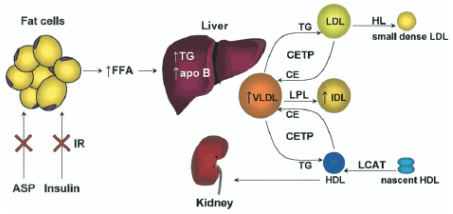
Visceral Fat Associates with Insulin Resistance



Adapted from Pouliot MC, et al. Diabetes 1992;41:826-834.

How Does Abdominal Obesity Cause Insulin Resistance





Metabolic syndrome and RA

Prevalence in early RA (<1 year of symptoms)

	Normal weight			Overweight/obese		
	Early RA	Control group	OR (95 %CI)	Early RA	Control group	OR (95 % CI)
	N = 36	*N* = 88		*N* = 55	*N* = 185	
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Metabolic syndrome	**6 (16.7)**	**2 (2.3)**	**5.6 (1.3–23.8)**[a]	26 (47.3)	91 (49.2)	0.9 (0.5–1.7)
Hypertension	**21 (58.3)**	**27 (30.7)**	**2.8 (1.3–6.0)**[a]	45 (81.8)	137 (74.1)	1.6 (0.7–3.3)
Abdominal obesity	3 (8.3)	2 (2.3)	3.9 (0.6–24.2)	40 (72.7)	131 (70.8)	1.1 (0.6–2.3)
Low HDL	4 (11.1)	11 (12.5)	0.7 (0.2–2.4)	19 (34.5)	56 (30.3)	1.2 (0.6–2.2)
High TG level	6 (16.7)	10 (11.4)	1.5 (0.5–4.6)	15 (27.3)	54 (29.2)	0.9 (0.4–1.7)
Hyperglycemia	**9 (25.0)**	**8 (9.1)**	**2.9 (1.0–8.0)**[a]	19 (34.5)	79 (42.7)	0.7 (0.4–1.4)

P-values <0.05 are marked in bold

[a] $P < 0.05$ Fisher's exact test

Müller R. Rheumatol Int. 2016.

Prevalence in northern Brazil

	Cases (n=314)	Controls (n=84)	p
Hypertension	46.7%	23.5%	<0.001
Type 2 diabetes mellitus	18.0%	6.2%	0.008
Family history of CVD	9.8%	4.8%	0.045
BMI	27.4 ± 4.8 kg/m2	25.9 ± 3.7 kg/m2	0.011
Waist circumference	93.7 ± 12.4 cm	87.1 ± 10.1 cm	<0.001
Smoking	5.6%	13.4%	0.014
Blood glucose	96.8 ± 33.5 mg/dl	87.1 ± 23.6 mg/dl	0.003
HDL	50.3 ± 13.5 mg/dl	56.3 ± 16.9 mg/dl	0.007
Prevalence of metabolic syndrome	51.3%	21.8%	<0.001

Poti Gomes KW. Mod Rheum. 2017, online May 09.

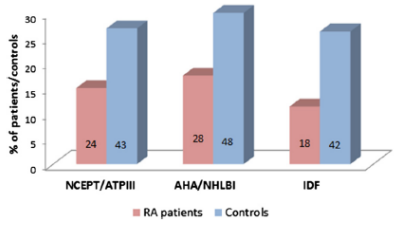
Multivariate logistic regression

Variables	OR (95% CI)	*p* Value
Age	1.04 (1.01–1.06)	**.009**
Dyslipidemia	1.89 (1.03–3.47)	**.040**
Sedentary lifestyle	2.36 (1.08–5.16)	**.031**
BMI	1.12 (1.05–1.20)	**<.001**
DAS28 ESR	1.23 (1.04–1.47)	**.016**

Bold values indicates $p < .05$.
OR: odds ratio; CI: confidence interval; BMI: body mass index; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate.

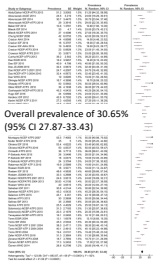
Poti Gomes KW. Mod Rheum. 2017, online May 09.

Prevalence in a cohort of Mexican Mestizo (early RA patients)

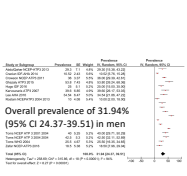


Parra-Salcedo F. Arthritis Res Ther. 2015;17:34

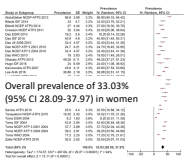
Prevalence meta analysis



Overall prevalence of 30.65% (95% CI 27.87-33.43)



Overall prevalence of 31.94% (95% CI 24.37-39.51) in men



Overall prevalence of 33.03% (95% CI 28.09-37.97) in women

Hallajzadeh J. PLos One. 2017;12:e0107361

Meta analysis

- Fasting blood glucose: 19.47% (95% CI 15.69-23.25)
- HDL: 41.78% (95% CI 28.73-54.84)
- Triglyceride: 28.43% (95% CI 22.3-34.57)
- Blood pressure: 48.65% (95% CI 41.03-56.26)
- Waist circumference: 52.63% (95% CI 43.76-61.5)

- OR for MS in RA patients is 1.44 (95% CI 1.20-1.74)

Hallajzadeh J. PLos One. 2017;12:e0107361

Mechanisms

- Inflammation
- Drugs such as glucocorticoids and NSAIDs
- Physical inactivity
- Altered body composition
- Insulin resistance
- Increased peripheral resistance (atherosclerosis)

Müller R. Rheumatol Int. 2016.

Metabolic syndrome in RA

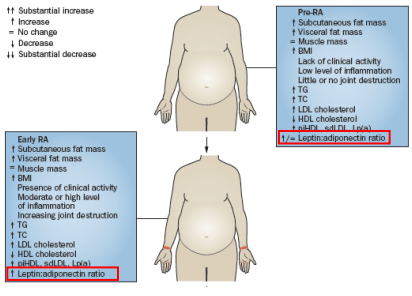
- MS may be different from that of the general population
- Metabolically obese phenotype
  - Lean body mass
  - Increased visceral adiposity
  - Normal or low BMI
- Changes in body composition appear early in RA

Müller R. Rheumatol Int. 2016.

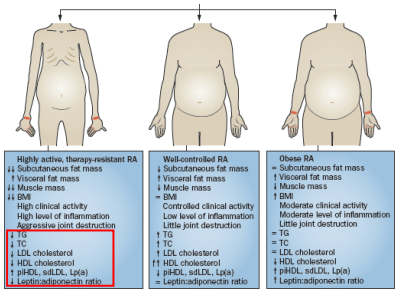
MS and RA

- They share…
  - Increase in free radicals
  - Deficiency of antioxidant systems
  - Increase in pro inflammatory cytokines
  - Endothelial damage
  - Formation and destabilization of atherosclerotic plaques

Medina G. Pharmacol Res. 2018; https://doi.org/10.1016/j.phrs.2018.01.009



Kerekes G. Nat Rev Rheum. 2014.



Kerekes G. Nat Rev Rheum. 2014.

Protective effect of obesity?

- Obese individuals with RA are commonly ACPA negative
- Reduce radiographic damage
  - Anabolic effects of leptin
  - Lower levels of adiponectin (proinflammatory in inflammatory conditions)
- Decreased CV mortality
- Based on retrospective studies

Kerekes G. Nat Rev Rheum. 2014.

Dyslipidemia: the RA lipid paradox

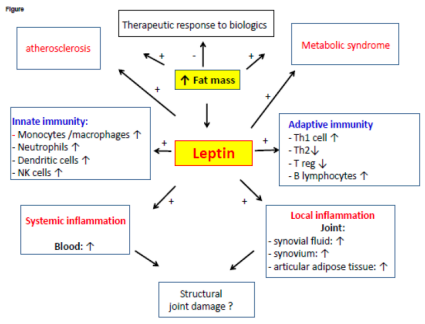
- In advanced RA,
  - Dysfunctional HDL
  - Small dense oxidized LDL that are more atherogenic
  - Increased levels of Lp(a)
- Lipid levels should be assessed after control of inflammation
- Traditional CV risk calculators do not take into account RA
  - Only one that includes **low grade** inflammation is Reynolds

Kerekes G. Nat Rev Rheum. 2014.

Leptin

- Higher plasma levels in patients with RA compared to controls
- Synovial fluid concentrations are lower than systemic but higher compared to those with osteoarthritis
  - Synovial fluid levels higher in those patients with erosive disease
- Some studies correlate leptin levels with disease activity
- Obesity and higher leptin levels may contribute to a higher inflammatory milieu that may confer resistance to some drugs such as infliximab

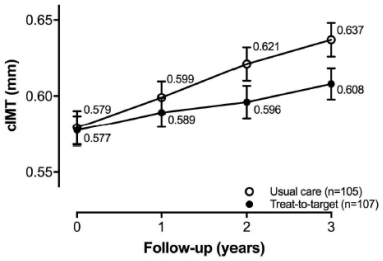
Toussirot E. Life Sci. 2015; doi: 10.1016/j.lfs.2015.05.001



Toussirot E. Life Sci. 2015; doi: 10.1016/j.lfs.2015.05.001

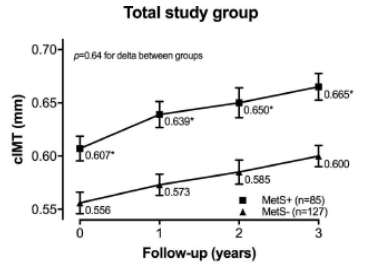
Consequences: type 2 DM and cardiovascular events

Progression of IMT



Burggraaf B. Atherosclerosis. 2018; doi: 10.1016/j.atherosclerosis.2018.02.019

Progression of IMT



Burggraaf B. Atherosclerosis. 2018; doi: 10.1016/j.atherosclerosis.2018.02.019

CV events

- 1176 RA patients
- 6.9% with CV events (MI, HF or stroke)
  - Higher than that reported for Italian general population

Multivariate analysis	OR	SE	P	CI 95%
Gender	3.46	0.29	<.001	1.94–6.18
Age	1.01	0.01	.202	0.99–1.04
Triglycerides	1.00	0.02	.159	0.99–1.08
Type 2 diabetes	2.32	0.31	.007	1.29–4.29
Metabolic syndrome	2.54	0.39	.005	1.29–4.52
High blood pressure	4.92	0.43	<.001	2.14–11.45
High disease activity	1.31	0.38	.003	1.15–1.68

Ruscitti P. Medicine. 2017;96:42(e8180)

Type 2 diabetes prevention

- No trials specific to patients with RA
- In population with glucose intolerance:
  - Intensive lifestyle modification: -58%
  - Metformin: -28%
  - Pioglitazone
  - Acabose
  - Metformin + rosiglitazone
- All these trials have assessed DM prevention, no hard endpoints

Type 2 diabetes prevention

- Who should be treated with metformin? (ADA)
  - In those with impaired fasting glucose (100-125 mg/dl) or glucose intolerance (2 h post 75 g glucose load 140-199 mg/dl) or Hba1c 5.7-6.4%
  - Specially for those:
    - BMI >35 kg/m2
    - Age <60 years
    - Prior history of gestational diabetes mellitus

Lifestyle modification

- Decrease caloric intake by 500 kcal per day
- Increase physical activity to 150 minutes per week
- Multidisciplinary approach
  - Dietitians
  - Physical therapists
  - Endocrinology
  - cardiology

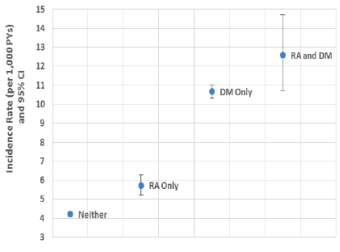
How should we assess CV risk and treat MS?

How should we calculate risk?

- Risk calculators designed for use in the general population do not accurately estimate the risk of CVD in patients with RA
- Specific calculators for patients with RA do not demonstrate improved performance compared to general calculators

Crowson CS. PLosOne. 2017;12(3):e0174656

RA equivalent to DM in CV risk?



Curtis JR. Arthritis Care Res. 2018 Feb 6 doi: 10.1002/acr.23535

EULAR recommendations

Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

Agca R. Ann Rheum Dis. 2017;76:17-28

Statins

- Consensus is that therapeutic response to statins in patients with RA is similar to that in general population
- Different cohorts have shown a reduced CV event rate in patients taking statins, although there are no specific RCT
- Who should be treated with statins? Should everybody be treated?
  - Probably not
  - High risk (multiple risk factors, DM, secondary prevention): if LDL >100 mg/dl
  - Intermediate risk (2 risk factors): if LDL >130 mg/dl
  - Low risk (0-1 risk factors): if LDL >160 mg/dl
- Subclinical atherosclerosis warrants treatment: atherosclerotic plaques, high IMT, high CAC

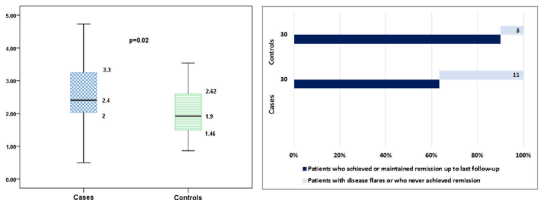
TRACE-RA

- RA patients >50 years or RA duration >10 years
- Endpoint: CV mortality, non fatal MI, stroke (excluding hemorrhagic), TIA, hospitalized angina, coronary and non coronary revascularization
- 2986 patients, randomized to atorvastatin 40 mg daily vs placebo
- More smokers in atorvastatin group (18.4 vs 14.5% p=0.019)
- Reduction in LDL 1.07 mmol (41.5 mg/dl)
- HR 0.66 (95% CI 0.40-1.11 p=0.119)
- Overall event was lower than anticipated (0.75% vs 1.8%) leading to early termination of the trial

Kitas GD. Ann Rheum Dis. 2015:74:688. SAT0105

Effect of MS on RA activity

Presence of MS was associated with a higher degree of disease activity in RA



Parra-Salcedo F. Arthritis Res Ther. 2015;17:34

RA therapy effects and CV outcomes

RA therapies

- Glucocoticoids:
  - Not clearly defined
  - It is really unknown if low dose treatment is associated with an increased risk
  - Moderate-high dose clearly increases risk due to effects in blood pressure, glucose, insulin resistance, lipid profile, weight, fat distribution
- Methotrexate:
  - Reduces CVD related mortality and morbidity
- Leflunomide:
  - Increases hypertension

Cavagna L. Med Inflam. 2012; doi:10.1155/2012/147354

RA therapies

- Cyclosporine:
  - Altered lipid metabolism
- Sulphasalazine:
  - No clear human data
- Hydroxycloroquine
  - Antithrombotic effect
  - Improves glucose and lipid profile
- TNF blockers:
  - Decrease incidence of CVD
  - Increase in HDL levels
  - Decrease in insulin resistance and resistin levels

Cavagna L. Med Inflam. 2012; doi:10.1155/2012/147354

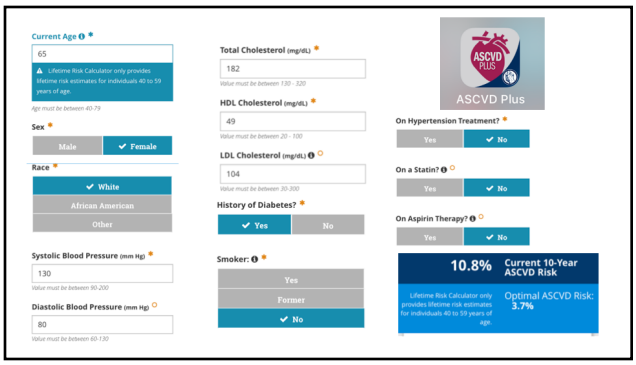
RA therapies

- NSAIDs
  - Increased incidence of CV disease with rofecoxib
  - Initial reports with lower risk with naproxen
  - Later studies show similar risk between ibuprofen, naproxen and celecoxib

Back to the case…

Clinical case

- 65 years old female patient, with RA treated with hydroxychloroquine
- Hypothyroidism diagnosed in 2016, treated with levothyroxine 50 ug per day
- Weight 69 kg, height 160 cm. BMI 26.95 kg/m2. BP 130/80 mm Hg
- Initial assessment (nov 2016), taking lovastatine 20 mg per day
  - Hba1c 6.6%
  - Total cholesterol 182 mg/dl
  - HDL 49 mg/dl
  - Triglycerides 150 mg/dl
  - LDL 103 mg/dl



In this patient…

- Type 2 diabetes
- Metabolic syndrome: blood glucose, low HDL, high triglycerides
- Cardiovascular risk:
  - Pooled cohort equation: 10.8%
    - If we increase 50%, as suggested by EULAR: 16.2%
  - She is at hight risk!
  - Despite having LDL of 103 mg/dl, she requires high intensity statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg per day) in order to have >50% decrease in LDL or achieve LDL target of <70 mg/dl

Conclusions

- MS confers a higher CV risk and progression to type 2 diabetes mellitus
- Patients with RA have an increased risk of MS, progression of atherosclerosis and CV events
- Traditional CV risk calculators underestimate CV risk in patients with RA
  - EULAR recommends increasing risk by 50%
- Lifestyle modification is essential to delay/prevent T2DM
- Management of CV risk factors (HTN, dyslipidemia) to decrease CV risk

Questions…

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This presentation can be downloaded in:

www.EndoDrChen.com