The Primary Care Guide To Understanding The Role Of The Metabolic Syndrome In Cognitive Decline Of Older Persons

1. Defining the Metabolic Syndrome

A Primary care practice often includes numerous patients who belong to "Club Metabolique"! Patients often want to achieve the health benefits of quitting a very non-exclusive, unhealthy club. The metabolic syndrome, previously termed "Syndrome X" or "insulin resistance syndrome" exists in 25% of the adult population (1). The metabolic syndrome includes central obesity, hypertension, dyslipidemia, and elevated insulin resistance with Type II diabetes and occurs in 40% of older persons. Several components of the metabolic syndrome are associated with increased risk of cognitive decline in later life (2). The relationship with hypertension, cardiovascular disease, and dementia is discussed in the cerebrovascular wellness segment **(CLICK HERE FOR MORE INFORMATION - DETA 2513.11)**. New second and third generation antipsychotic medications may also produce metabolic syndrome in adults with no previous evidence for this condition. Routine monitoring is recommended for these patients **(See Table 2)**. *A patient handout on the price of the Metabolique Club membership is included in this packet- 2513.95, 2513.96.*

Table 1. CLUB METABOLIQUE
NCEP III Definition of Metabolic Syndrome
(includes 3 of 5 features)

1.	Abdominal obesity	M>40 in. F>35 in.
2.	Low HDL-C levels	M<40 mg/dl F<50 mg/dl
3.	High triglyceride level	>150mg/dl
4.	Hypertension	Systolic >130 Diastolic > 85
5.	↑ Fasting BS	>110 mg/dl

Arch Int. Med 2002;162:2033-36

2513.94. Metabolic Syndrome

Table 2
Basic Monitoring of Metabolic Effects In Persons Receiving Antipsychotic Medications

	Priority to therapy	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

2513.94. Metabolic Syndrome

The National Cholesterol Education Program III (NCEP) guidelines define metabolic syndrome as the existence of three of five risk factors identified in **Table 1**. These risk factors include obesity, low HDL-C levels, elevated triglycerides, systolic or diastolic hypertension and elevated fasting blood sugar levels. Some values are adjusted for male versus female. Ancillary features not included in the definition include evidence of chronic mild inflammation as seen with elevated serum levels of C-reactive protein, as well as enhanced oxidative stress, thrombophilia, and endothelial dysfunction *(Click here for more information about inflammation and dementia – 2513.81).* Each of these diagnostic features has specific available, safe, therapeutic interventions. Many of the ancillary features of the metabolic syndrome are identified as risk factors for the development of dementia and metabolic syndrome in later life is associated with Alzheimer's disease (7).

2. Risk Factors for Metabolic Syndrome

The risk for metabolic syndrome increases with age and is enhanced in African American citizens, as well as those with less than a high school education (3). Menopause increases the risk for metabolic syndrome by 60%, as well as psychological stress that may increase plasma cortisol levels (1). The risk for metabolic syndrome increases 23% per 10 pounds of weight gained in older persons; however, the overall risk is reduced with regular exercise. Elders with metabolic syndrome were more likely to have cognitive impairment, especially those with evidence of a systemic inflammatory marker such as creative protein (4), (7). Metabolic syndrome is also identified as a significant risk factor for silent brain infarction in otherwise healthy persons (5).

Recent studies discuss lack of exercise and midlife obesity as risk factors for the development of dementia in later life (6), (8) *(Click here for more information - 2513)*. Central obesity in midlife is a significant risk factor for metabolic syndrome **(See Table 3)**. Obesity increases the likelihood of dementia, reduces life expectancy **(See Table 4)** and increases the risk for Type II diabetes, as well as cerebrovascular disease; however, the definition of obesity may be less stringent in the elderly than younger adults (26). Obesity and other risk factors for metabolic syndrome are common health problems in many nations and cultures **(See Table 5).**

Table 3. Definitions of Weight / BMI

Category	BMI
Underweight	<18.5
Normal	18 to 25
Overweight	25 to 30
Obesity	>30

Table 4. Excess Deaths in the U.S. Caused by Obesity (19)

BMI	Excessive Deaths Per Year
< 18.5	+33,746
18 to 25	Baseline comparison
25-30	-86,094
>30	+111,909

JAMA 2005 Apr 20;293(15):1861-7

Table 5. Prevalence of Cardiovascular Risk Factors that may Impact Cerebrovascular Health in Adults

Nation	n	Impact on Population in each Country	Ref
Canada	2237	57% one or more metabolic risk factors 29% BMI >25, 51% sedentary life style	20
Canada	1844	33% altered metabolic profile and only one-third normal	21
Spain	704	42% of HBP not detected 21% of HBP adequately controlled	22
Ireland	1018	One-half overweight and ¼ obese, and 40% sedentary	23
Sey Chelles	1255	25% obese and 22% demonstrate metabolic syndrome	24

Newer data suggests that Type II diabetes in older persons may be a risk factor for the development of dementia (9), although the precise mechanism for this connection is unclear *(Click here for more information – 2513.92)*. Increased peripheral resistance to insulin may expose the brain to excessive levels of circulatoring insulin which can alter insulin sensitive receptors in the brain (10), (11), (12). Diabetes is a demonstrated risk factor for atherosclerotic cardiovascular and cerebrovascular disease, as well as dementia. The role of dyslipidemia in the pathogenesis of Alzheimer's disease is unclear despite the fact that the presence of APO- lipoprotein Type 4 alleles is a risk factor for dementia. Neither the levels of total cholesterol nor high density lipoprotein in late life are consistently correlated to risk of subsequent cognitive decline (13).

3. **Understanding the Impact of Metabolic Syndrome on Cognitive Function in Later Life**
The metabolic syndrome may alter risks for dementia based on a direct impact caused by specific pathologies including: 1) deposition of amyloid, 2) acceleration of vascular pathology, 3) accelerated production of neurofibrillary tangles, 4) enhanced inflammatory response, or 5) a combination of all the above. Although scientists cannot precisely explain the interaction of metabolic syndromes and dementia, clinicians are justified in linking long-term intellectual function to management of risk factors for metabolic syndrome including obesity, hypertension, and hyperlipidemia.

The protective effect of statin therapy remains controversial with multiple studies showing protection (14), (15) and a few studies disputing this beneficial effect (16). Statins may reduce cardiovascular morbidity and this benefit may protect cognition (17), (18), **(Click here for more information about statin use and dementia – 2513.911).** Prophylactic use of statins in persons with normal lipid profiles is not recommended as a preventive intervention **(See Table 5.)**

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Table 5. **Conclusions About Metabolic Syndrome**

Symptom	Independent Risk Factor for Dementia	Recommended Intervention	Exercise Improves
↑ Blood Sugar	Yes	↓ BS, ↓ weight, meds	✓
↑Triglycerides	?	Diet, meds	✓
Low LDL Cholesterol	?	Diet, meds	✓
Hypertension	Yes	Meds	✓
Obesity	Yes	Diet	✓
Meds-appropriate medications **Diet**-dietary management			

Understanding the role of the metabolic syndrome in dementia   17

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4. Treating Metabolic Syndrome in Adults
The metabolic syndrome is a collection of disorders that often produce disease that is greater than the sum of the individual pathogenesis (27). Weight control, exercise and blood sugar management are central features of management (18) **(See Table 5).**

(Click here for more information about on the role of diabetes in dementia – 2513.911).

Recommendations For Primary Care Physicians
1. Screen for metabolic syndrome in adults.
2. Promote exercise on a daily basis for all adults.
3. Encourage weight control as a component of cognitive wellness.
4. Treat each component of the syndrome to achieve maximum management.
5. Explain the potential impact of metabolic syndrome on cognitive function to the older patient.

REFERENCES

1. Hazzard WB, Blass JP, Halter JB, et al (Eds.) (2003), *Principles of geriatric medicine and gerontology* (5th Edition). New York: McGraw-Hill.

2. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer's disease. Arch Neurol 2005;62(10):1556-60.

3. Carnethon MR, Loria CM, Hill JO, et al. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985-2001. Diabetes Care 2004;27(11):2707-15.

4. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292(18):2237-42.

5. Kwon HM, Kim BJ, Lee SH, et al. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37(2):466-70.

6. Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504): 1360.

7. Razay G, Vreugdenhil A, Wilcock G. The metabolic syndrome and Alzheimer disease. Arch Neurol 2007;64:93-96.

8. Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504): 1360.

9. Biessels GJ, Kappelle LJ, Utrecht Diabetic Encephalopathy Study Group. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 2005;33(Pt 5):1041-4.

10. Frolich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 1998;105:423-438.

11. Fishel MA, Watson GS, Montine TJ, et al. Hyperinsulinemia provides synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol 2005;62(10):1539-44.

12. Vanhanen M, Koivisto K, Kuusisto J, et al. Cognitive function in an elderly population with persistent impaired glucose tolerance. Diabetes Care 1998;21(3):398-403.

13. Li G, Shofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer's disease: a community-based cohort study. Neurology 2005;65(7):1045-50.

14. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000;356:1627-31.

15. Rockwood K, Kirkland S, Hogan D, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59:223-227.

16. Zandi P, et al. Do statins reduce the risk of incident dementia and Alzheimer's disease? The Cache County Study. Arch Gen Psych 2005;62:217-224.

17. Bonora E. The metabolic syndrome and cardiovascular disease. Ann Med 2006;38(1): 64-80.

18. Bestermann W, Houston MC, Basile J, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, Part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the

metabolic syndrome. Am J Med Sci 2005;329(6):292-305.

19. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293(15):1861-7.

20. Joffres MR, Titanich KL, Hessel PA. The Alberta Heart Health Survey: methods and results. Can J Cardiol 1993;9(4):300-8.

21. Scarsella C, Almeras N, Mauriege P, et al. Prevalence of metabolic alterations predictive of cardiovascular disease risk in the Quebec population. Can J Cardiol 2003;19(1):51-7.

22. Plans P, Pardell H, Salleras L. Epidemiology of cardiovascular disease risk factors in Catalonia (Spain). Eur J Epidemiol. 1993;9(4):381-9.

23. Creagh D, Neilson S, Collins A, et al. Established cardiovascular disease and CVD risk factors in a primary care population of middle-aged Irish men and women. Ir Med J 2002;95(10):298-301.

24. Bovet P, Shamlaye C, Gabriel A, et al. Prevalence of cardiovascular risk factors in a middle-income country and estimated cost of a treatment strategy. BMC Public Health 2006;6:9.

25. Leiter LA, Abbott D, Campbell NR, et al. Lifestyle modifications to prevent and control hypertension. Recommendations on obesity and weight loss. CMAJ 1999;160(9 Suppl):S7-12.

26. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. Arch Intern Med 2001;161(9):1194-203.

27. Firdaus M, Mathew MK, Wright J. Health promotion in older adults: The role of lifestyle in the metabolic syndrome. Geriatrics 2006;61(2):18-25.