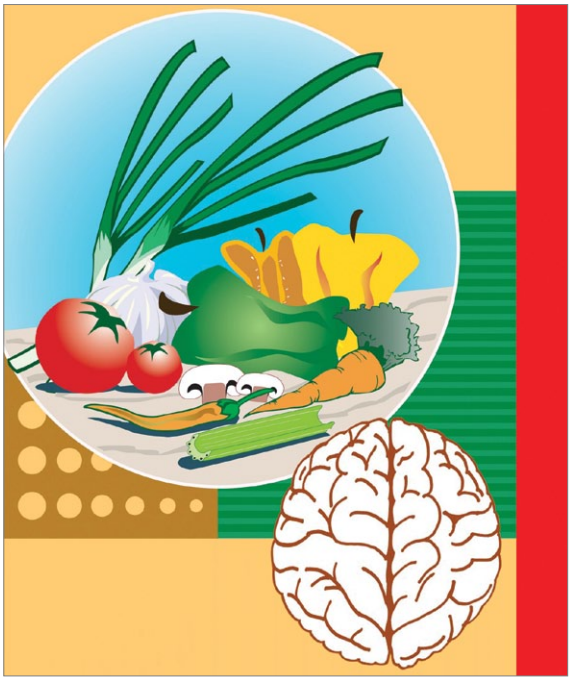
Metabolic disturbance and dementia: A modifiable link

Dietary changes to correct hyperinsulinemia might slow cognitive decline

In addition to increasing patients' risk for cardiovascular disease, stroke, and cancer, obesity and metabolic disturbance contribute to age-related cognitive decline and dementia. In particular, insulin resistance and hyperinsulinemia promote neurocognitive dysfunction and neurodegenerative changes during the extended, preclinical phase of Alzheimer's disease (AD). However, with dietary modification it may be possible to resensitize insulin receptors, correct hyperinsulinemia, and improve memory function.



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Metabolic disturbance and neurodegeneration

In the United States, 5.4 million people have AD, and there will be an estimated 16 million cases by 2050.[1] Simultaneously we are experiencing an epidemic of metabolic disturbance and obesity. Approximately, 64% of adults in the United States are overweight (body mass index [BMI]: 25.0 to 29.9 kg/m^2) and 34% are obese (BMI: ≥30 kg/m^2).[2] By 2030, 86% of adults will be overweight and 51% will be obese.[3] This confluence of epidemics is not coincidental but instead reflects the fact that metabolic disturbance is a fundamental factor contributing to cognitive decline and neurodegeneration.[4]

Ninety-six percent of AD cases are classified as late onset, sporadic AD, occurring after age 64.[1] Mild cognitive impairment (MCI) is a clinical construct that entails greater than expected memory impairment for the patient's age and identifies older adults who are at increased risk for dementia. MCI represents the first clinical manifestation of neurodegeneration for a subset of patients who will progress to AD.[5,6] MCI is distinguished from age-associated memory

Table

Waist circumference and metabolic factors in 122 older adults with MCI[a]

Metabolic indicator	Value
Mean (SD) fasting glucose, mg/dL	99.5 (11.2)
Mean (SD) fasting insulin, μIU/mL	15.2 (8.1)
Mean (SD) waist, cm	96.4 (13.3)
Waist-insulin correlation	$r = 0.51$, $P < .001$

[a]Older adult patients (age ≥68) with subjective memory complaints were recruited from the community and screened with instruments assessing everyday functioning and objective memory performance to establish the presence of MCI

MCI: mild cognitive impairment; SD: standard deviation

Clinical Point

BMI and fasting insulin are positively correlated with atrophy in frontal, temporal, and subcortical brain regions

impairment (AAMI), which originally was conceptualized as normal or benign memory decline with aging.[7,8] Recent data indicate that Alzheimer's-type neuropathologic changes are the basis for subjective memory complaints and objectively assessed age-related cognitive decline,[9] and early neurodegeneration is present in many patients with AAMI or MCI.[10] This is consistent with the idea that an extended preclinical phase precedes AD onset. The preclinical phase can persist for a decade or more and precedes MCI and overt functional decline. However, neuropathologic changes accumulate during the preclinical phase of AD[11] and during the preclinical phase of type 2 diabetes mellitus (T2DM).

Hyperinsulinemia and dementia

Insulin resistance and hyperinsulinemia occur in >40% of individuals age ≥60 and prevalence increases with age.[4,12] Hyperinsulinemia develops to compensate for insulin resistance to overcome receptor insensitivity and maintain glucose homeostasis. Insulin receptors are densely expressed in brain regions vulnerable to neurodegeneration, including the medial temporal lobe and prefrontal cortex, which mediate long-term memory and working memory. However, insulin must be transported into the CNS from the periphery because little is synthesized in the brain. Paradoxically, peripheral compensatory *hyper*insulinemia resulting from insulin resistance is associated with central (brain) *hypo*insulinemia because of insensitivity and saturation of the receptor-mediated blood-brain barrier transport mechanism.[13-15]

Hyperinsulinemia is the precursor to T2DM. However, hyperinsulinemia is not well recognized in clinical contexts and generally is not a treatment target. Nonetheless, it contributes to several health problems, and insulin resistance in middle age is associated with age-related diseases such as hypertension, coronary artery disease, stroke, and cancer, while insulin sensitivity protects against such disorders.[16]

Chronic insulin resistance may contribute more to dementia development than T2DM because of the extended period of hyperinsulinemia that precedes T2DM onset. In population studies,[17] insulin resistance syndrome increases risk for developing AD independent of apolipoprotein E (APOE e4) allele status, and in a longitudinal study,[18] the risk for AD solely attributable to peripheral hyperinsulinemia was up to 39%. Being overweight in midlife increases risk for dementia in late life, and APOE e4 allele status does not contribute additional risk after accounting for BMI.[19] Middle-aged individuals with hyperinsulinemia show memory decline, and obesity in middle age was associated with greater cognitive impairment after 6-year follow-up.[20] Even in older adults who seem cognitively unimpaired, BMI and fasting insulin are positively correlated with atrophy in frontal, temporal, and subcortical brain regions, and obesity is an independent risk for atrophy in several brain regions, including the hippocampus.[21]

Compared with healthy older adults, individuals with AD have lower ratios of cerebrospinal fluid to plasma insulin.[22] This lower ratio reflects the peripheral-to-central gradient of insulin levels in AD

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establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **Adverse Reactions Reported With Other SNRIs-** Although the following are not considered adverse reactions for desvenlafaxine succinate, they are adverse reactions for other SNRIs and may also occur with desvenlafaxine succinate: gastrointestinal bleeding, hallucinations, photosensitivity reactions and severe cutaneous reactions (such as Steven-Johnson Syndrome, toxic epidermal necrolysis, and/or erythemia multiforme). **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **Drug-Laboratory Test Interactions-** False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [*see Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.12)*]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [*see Clinical Pharmacology (12.6)*].

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

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and suggests an etiological role for such metabolic disturbance. Insulin resistance has downstream effects that potentiate neurodegenerative factors, and central hypoinsulinemia can accelerate neurodegenerative processes and cognitive decline.[4,23] Brain insulin plays a direct role in regulating proinflammatory cytokines and neurotrophic and neuroplastic factors essential for memory function. Insulin degrading enzyme, which varies with insulin levels,[24] regulates the generation and clearance of amyloid β (Aβ) from the brain.[25]

Hyperinsulinemia typically is evident in increasing waist circumference and body weight.[26] Waist circumference of ≥100 cm (39 inches) is a sensitive, specific, and independent predictor of hyperinsulinemia for men and women and a stronger predictor than BMI, waist-to-hip ratio, and other measures of body fat.[27] Unpublished data derived from our clinical research with MCI subjects supports the association of metabolic disturbance with age-related cognitive decline. Our subjects are recruited from the community on the basis of mild memory decline and—other than excluding those with diabetes—weight and metabolic status are not considered in evaluating individuals for enrollment. The ***Table*** (***page 18***) contains data on waist circumference and metabolic function in 122 older adults (age ≥68) with MCI. On average, these individuals exhibited fasting insulin values in the hyperinsulinemia range and elevated fasting glucose levels that indicated borderline diabetes. Waist circumference also was high, indicating excessive visceral fat deposition. We also observed a relationship between waist circumference and insulin, a consistent observation in older adults with memory decline. These data would not be surprising in any sample of older adults because of the population base rates for these conditions. However, we also found that waist circumference was a significant predictor of memory performance in patients with MCI. Abdominal adiposity is highly correlated with intrahepatic fat.[28] Given this and recent indications that Alzheimer's-type neuropathologic factors are generated in the liver,[29,30] the predictive value of waist

Insulin resistance and dementia

Related Resources

- Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 2004;3(3):169-178.
- Luchsinger JA, Tang MX, Shea S, et al. Hyperinsulinemia and risk of Alzheimer's disease. Neurology. 2004; 63(7):1187-1192.
- Krikorian R, Shidler MD, Dangelo K, et al. Dietary ketosis enhances memory in mild cognitive impairment. Neurbiol Aging. 2012;33(2):425.e19-e27.

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circumference to memory performance may reflect the fact that it is a proxy for downstream actions of liver fat.

Clinical Point

Reducing insulin by restricting calories or maintaining a ketogenic diet has been associated with improved memory function

Dietary interventions

There is no cure for dementia, and it is not clear when effective therapy might be developed. Prevention and risk mitigation represent the best means of reducing the impact of this public health problem. Researchers have proposed that interventions initiated when individuals have predementia conditions such as AAMI and MCI might stall progression of cognitive decline, and MCI may be the last point when interventions might be effective because of the self-reinforcing neuropathologic cascades of AD.[31] Because central hypoinsulinemia may promote central inflammation, Aβ generation, and reduced neuroplasticity, approaches aimed at improving metabolic function (and in particular correcting hyperinsulinemia) could influence fundamental neurodegenerative processes. Dietary approaches to preventing dementia are effective, low-risk, yet underutilized interventions. Reducing insulin by restricting calories[32] or maintaining a ketogenic diet[33] has been associated with improved memory function in middle-aged and older adults.

Carbohydrate consumption is the principal determinant of insulin secretion. Eliminating high-glycemic foods, including processed carbohydrates and sweets, would sensitize insulin receptors and correct hyperinsulinemia. In addition, replacing high glycemic foods with fruits and vegetables would increase polyphenol intake. Epidemiologic evidence supports the idea that greater consumption of polyphenol-containing vegetables and fruits mitigates risk for neurocognitive decline and dementia.[34,35] Preclinical evidence suggests that such protection may be related to neuronal signaling effects and anti-inflammatory and antioxidant actions.[36] In addition, certain polyphenol compounds, such as those found in berries, enhance metabolic function.[37,38] In a 12-week pilot trial, older adults with early memory changes (N = 9, mean age 76) who drank supplemental blueberry juice showed enhanced memory and improved metabolic parameters.[39]

Dietary changes that preserve insulin receptor sensitivity can help ensure general health with aging and substantially mitigate risk for neurodegeneration. The Western diet is particularly insulinogenic and dietary habits are difficult to change. However, the substantial benefits, absence of adverse effects, and low cost make dietary intervention the optimal means of protecting against neurodegeneration and other age-related diseases. Embarking on such a program early in life would be best, although late-life intervention can be effective.

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Bottom Line

Insulin resistance and hyperinsulinemia drive neurodegeneration and increase risk for age-related cognitive decline and dementia. In the absence of effective pharmacotherapy, nutritional approaches that correct hyperinsulinemia offer the possibility of slowing or preventing progression of cognitive decline. Correcting hyperinsulinemia by eliminating high-glycemic carbohydrate foods may be the most robust intervention available to reduce dementia risk.

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Clinical Point

Greater consumption of polyphenol-containing vegetables and fruits might mitigate risk for neurocognitive decline and dementia