
図2　国立国際医療研究センター病院　糖尿病・代謝症候群診療部のホームページ
(http://ncgm-dm.jp/naibunpitu/index.htm)
赤枠の部分から「糖尿病標準診療マニュアル」にアクセスできる。

血糖コントロール目標値は安全性と効果の実証を重視してHbA1c(JDS値)6.5％未満(空腹時血糖値130mg/dL未満，食後2時間血糖値180mg/dL未満)とした。糖尿病治療薬に関しては，細小血管症(糖尿病網膜症・腎症・神経障害)だけでなく大血管症(冠動脈疾患・脳卒中・末梢動脈疾患)の予防実証の観点から薬剤を選択した(図3，表1)。特にメトホルミンは，大血管症予防や死亡率低下(日本人を含む)が示されている唯一の薬剤であり，日本人(特に男性)の肥満者増加傾向(図4)を鑑みて日本でもその有効性が期待される。

なお，本マニュアルは個々の臨床状況での理論・経験に基づく医師の判断を拘束したり特定の方向付けを強制したりするものではなく，参考となる診療補助情報として活用されるべきものである。

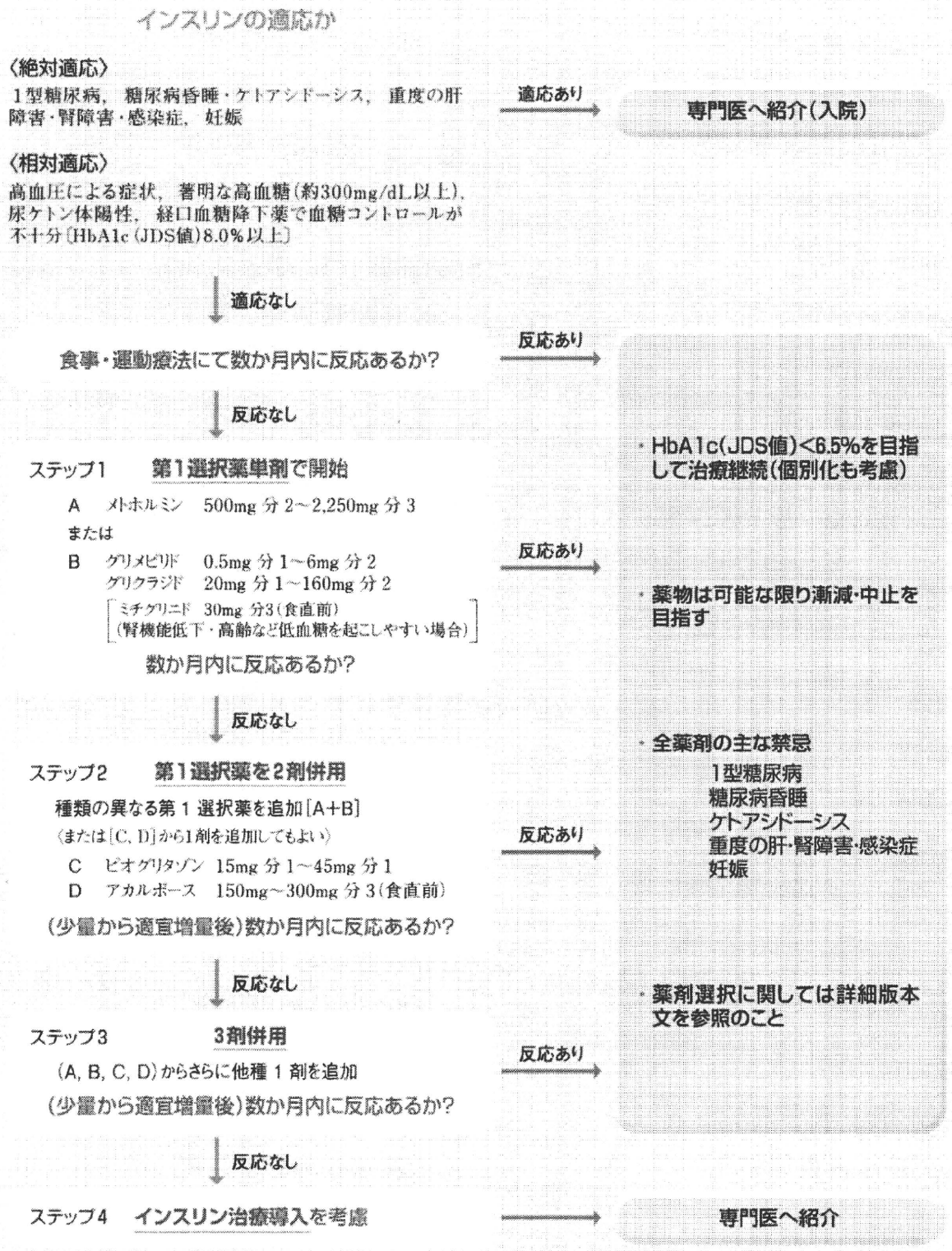


図3 糖尿病治療の流れ
薬剤選択は血管合併症に対するエビデンスの有無により判断した。
(国立国際医療研究センター病院 糖尿病標準診療マニュアルより)

表1　経口糖尿病治療薬の特徴とエビデンス
〔国立国際医療研究センター病院 糖尿病標準診療マニュアル（一般診療所・クリニック向け）より一部改変〕

| 作用 | 種類 | 主な副作用 | 体重増加 | 主な禁忌 | 合併症予防効果 | |
|---|---|---|---|---|---|---|
| | | | | | 細小血管症 | 動脈硬化性疾患 |
| インスリン抵抗性改善 | ビグアナイド薬 | 乳酸アシドーシス[1]，胃腸障害 | なし | 乳酸アシドーシスの既往，低酸素血症[*] | ○ | ○[2] |
| | チアゾリジン薬 | 浮腫，心不全，骨折 | あり | 心不全[*] | | △[3] |
| インスリン分泌促進 | スルホニル尿素薬 | 低血糖，肝障害 | あり | [*] | ○ | △[3] |
| | グリニド系薬 | | | [*] | | |
| 食後高血糖改善 | α-グルコシダーゼ阻害薬 | 肝障害，胃腸障害（放屁・下痢・腹満・便秘） | なし | [*] | | △[3] |
| その他 | DPP4阻害薬 | 胃腸障害 | なし | [*] | | |

[*] 全剤共通：1型糖尿病，糖尿病昏睡・ケトアシドーシス，重度の肝障害・腎障害・感染症，妊娠（インスリン治療の絶対適応である。）
○：実証あり。　△：実証はないが示唆されている。
[1] 適正使用条件下ではリスクは増加しない。　[2] 臨床研究による実証あり。
[3] 効果の可能性が示唆されているが実証されていない。

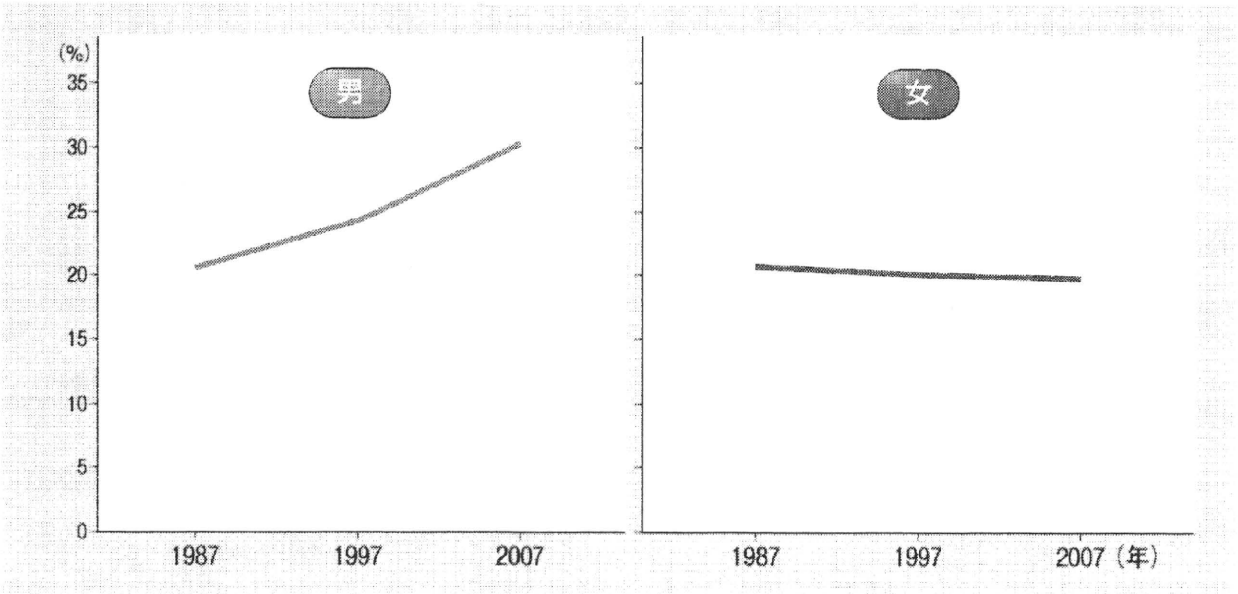


図4　日本人肥満者（BMI25以上）の割合の年次推移
（厚生労働省．国民健康栄養調査結果2007より）

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**COMMENTARY**

# Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

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## Abstract

Recent studies have revealed that type 2 diabetes mellitus (T2DM) is a risk factor for cognitive dysfunction or dementia, especially those related to Alzheimer's disease (AD). Basic research suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. We and others have reported that small vessel diseases affect cognitive function in older diabetics. Asymptomatic ischemic lesions in T2DM subjects may lower the threshold for the development of dementia and this may explain the inconsistency between the basic research and clinicopathological studies. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and magnetic resonance imaging may elucidate these issues. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the role of insulin in the processing and deposition of Aβ. Vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia.

**Keywords:** *Alzheimer's disease, ischemic lesions, dementia, insulin, Aβ*

The prevalence of type 2 diabetes mellitus (T2DM) increases with age, and dementia also increases its incidence in later life. Therefore, the coincidence of T2DM and dementia increases with ageing. Moreover, recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia [1]. There is ample evidence that T2DM is related not only to vascular dementia but also to clinical diagnosis of Alzheimer's disease (AD)-type dementia [2]. The precise mechanisms underlying T2DM-related cognitive dysfunction or development of dementia, especially AD-type dementia, remain to be elucidated, although several hypothetical mechanisms have been proposed. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation endoproducts, which have potentially toxic effects on neurons. Diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic.

T2DM, especially in conjunction with obesity, is characterised by insulin resistance and/or hyperinsulinaemia. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiological effects of circulating insulin, and often is accompanied by raised insulin levels. Basic research suggests that insulin accelerates AD-related pathology through its effects on the amyloid beta (Aβ) metabolism and tau phosphorylation [2]. Insulin reportedly raises Aβ concentrations in plasma in AD subjects, and these effects may contribute to the risk of AD in T2DM. The desensitization of insulin receptors, insulin resistance, reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE). IDE degrades Aβ as well as insulin, and reduced amounts of IDE may result in greater

amyloid deposition. Less insulin signalling may also induce increased activity of glycogen synthase kinase-3β, which leads to the enhanced phosphorylation of tau protein and the formation of neurofibrillary tangles (NFTs). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. One study demonstrated that diabetics show significantly less AD-associated neuropathology [3], while another failed to show any relationship between diabetes and AD-associated neuropathology [4]. Why does this disparity exist between clinicopathological data and the implications of basic research?

AD has been thought to be a neurodegenerative disorder, which can be sharply distinguished from vascular dementia. Recent studies, however, suggest that the distinction between AD and vascular dementia may not be tenable. There is now substantial and growing evidence that vascular disorders and/or impaired cerebral perfusion contribute to the development of sporadic AD. For example, cerebrovascular pathology including stroke seems to play an important role in the eventual development of the clinical symptoms of AD [5].

On cerebral magnetic resonance imaging (MRI), white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). These lesions are frequently concomitant with Alzheimer-related neuropathology (senile plaques and NFTs) and contributes to cognitive impairment in AD subjects [6]. We previously reported that small vessel diseases affect cognitive function in older diabetics who have not developed either overt dementia or symptomatic stroke [7, 8]. The number of asymptomatic infarcts and the extent of white matter lesions in the brain detected with MRI were found to be associated with the scores of several cognitive functional tests, especially the digit symbol substitution test, a neurocognitive test that primarily reflects declines in perceptual speed. We also reported that an inflammatory cytokine, tumour necrosis factor-α, which is a risk factor for atherosclerosis, is related to cognitive dysfunction in older nondemented diabetics [9]. A recent study demonstrated that T2DM subjects with clinical diagnosis of dementia have less Alzheimer-related pathology but more ischaemic lesions [10]. This supports the hypothesis that small vessel disease lowers the threshold for the development of dementia. That is, if subjects have the same level of cognitive dysfunction, those with a combination of two types of pathologies have fewer pathological changes in each of their pathologies than those with a single pathology which is severe enough to cause the cognitive dysfunction. Therefore, these pathological reports do not necessarily refute the possibility that DM accelerates the development of Alzheimer-related neuropathology in the patients with clinical diagnosis of dementia. Arvanitakis *et al.* demonstrated in 2004 that T2DM increases the incidence of AD by clinical diagnosis [11], but T2DM ameliorated perceptual speed but not global cognition. A previous study [12] and our own studies [7, 8] showed that cerebral ischaemic lesions are preferentially associated with a lower measure of perceptual speed. These results also suggest that small vessel disease contributes to cognitive decline in these populations.

Hypertension is often accompanied by diabetes, and several longitudinal studies appear to support the notion that hypertension predisposes to cognitive decline and the development of dementia [13]. Vascular alterations induced by high blood pressure may contribute to cognitive dysfunction. Hypertension is also associated with cerebrovascular disease including lacunar brain infarcts and white matter lesions, which may contribute to cognitive impairment in diabetics.

Recently, amyloid imaging technology with positron emission tomography, which visualises Aβ depositions in the human brain, has been developed and is now widely available [14] although some limitations of resolution and specificity still exist. This technology can be used to investigate the relative contributions of ischaemic and neurodegenerative changes to the increasing development of dementia in T2DM subjects. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and MRI may help to elucidate these issues, especially with higher field MRI with some potential for the imaging small vessel diseases [15] as well as diffusion tensor imaging method [16]. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischaemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the hypothesis that insulin plays a role in the processing and deposition of Aβ. These investigations are important considering the future availability of disease-modifying therapeutics such as Aβ vaccination and inhibitors for Aβ secretions.

At present, vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. Vascular risk factors including diabetes and hypertension are reportedly associated with the progression of lacunae and white matter lesions [17]; however, the beneficial effects on cognitive function of pharmaceutical interventions with antidiabetics and antihypertensives are less clear in terms of the inhibition of the progress of lacunae and white matter lesions. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia. If such protective effects do exist, the underlying mechanism of the therapeutic effects should be interesting, whether it relies on the inhibition of the development of vascular lesions or in that of the neurodegenerative process.

With the current increase in the older population, T2DM-associated cognitive dysfunction and dementia are an increasingly larger problem. A greater understanding of the relevant pathophysiology and the establishment of better therapeutic interventions are urgent issues.

## Key points

- Ischaemic lesions including lacunae and white matter lesions affect cognitive function in diabetic older people.
- The relative pathological contribution in diabetes-related cognitive dysfunction of vascular changes and neurodegenerative processes merits further investigation.
- Further studies are warranted to determine whether medical interventions on vascular risk factors have protective effects against cognitive function in diabetics.

## Conflict of interest

None to declare.

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