Clinical Article

Hyperinsulinemia, Insulin Resistance and Cognitive Decline in Older Cohort*

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Abstract

Objective Type 2 diabetes has been recently recognized as an important risk factor for cognitive decline of patients with Alzheimer's disease (AD). But the roles of hyperinsulinemia (HI) and insulin resistance (IR) in the development of AD are still controversial. This study was designed to evaluate whether HI or IR influenced the cognitive functions of older cohort.

Methods The cognitive functions of 328 consecutive elderly patients were evaluated with a battery of cognitive rating scales. Their fasting blood glucose (FBG) and fasting insulin (FINS) were analyzed and IR was calculated with modified-Homa. The cognitive scores in different groups and the correlation of cognitive functions with HI or IR were analyzed.

Results In our study, there were 180 participants with HI and 148 without HI, and 192 with IR and 136 without IR. The participants with HI showed worse cognitive functions than those without HI in MMSE, MOCA, CDR, orientation, delayed memory, and attention/calculation domains. Similarly, the elderly with IR had lower cognitive scores than those without IR in MMSE, MOCA, CDR, GDS, orientation, delayed memory, and attention/calculation domains. The insulin levels and Homa IR had negative correlation with the scores of MMSE and delayed memory, not only in the model 1 adjusted for FBG and diabetes history, but also in the model 2 adjusted for all nine demographic characteristics.

Conclusion HI and IR are important risk factors for cognitive decline of the elderly, especially for the dysfunctions in delayed memory domains.

Key words: Cognitive function; Alzheimer's disease; Hyperinsulinemia; Insulin resistance

Biomed Environ Sci, 2012; 25(1):8-14 *doi: 10.3967/0895-3988.2012.01.002* *ISSN:0895-3988*

www.besjournal.com(full text) *CN: 11-2816/Q*

INTRODUCTION

Type 2 diabetes and its related metabolic disorders, such as hyperinsulinemia (HI), insulin resistance (IR) and hyperglycemia, are important conditions among the elderly. Some recent studies have discovered that the insulin metabolic disorders might be one of the important risk factors for Alzheimer's disease (AD). Some researchers believe that, independent of the glucose effect, the level of insulin is associated with cognitive decline in the old people[1-2]. Compared to normal adults, the adults with IR had obvious cognitive decline under long-term observation[3]. However, some researchers presented negative evidence that the relation between IR and cognitive dysfunction was not clear[4-5]. Several other studies have reported that type 2 diabetes and its related

*This study was supported by the Medical College Natural Science Foundation of Shanghai Jiao Tong University (09XJ21028) and the Shanghai Jiaotong University Interdisciplinary Study Foundation Medicine and Engineer.

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Received: March 3, 2011; Accepted: July 6, 2011

metabolic disorders are related to vascular dementia (VaD), rather than AD[6-7]. In view of the conflicting results and the clinical demand, our current study is to observe the cognitive functions of the elderly with different levels of insulin and at various statuses of IR. Moreover, we will analyze the association between HI, IR and the functions of various cognitive domains, including orientation, immediate memory, delayed memory, attention/calculation, and linguistic capacity. The primary aim of our study is to determine whether insulin metabolic disorder is associated with cognitive dysfunctions among elderly adults, which will provide a helpful information for prevention and treatment of cognitive decline among them.

METHODS

Study Population

Participants were patients or outpatients from our Geriatric Department of the Sixth People's Hospital, affiliated to the Shanghai Jiao Tong University. The study was conducted from July 2008 to July 2010, which was approved by the Medical Ethics Committee of the Shanghai Jiao Tong University. All individuals signed an informed written consent. Finally 328 participants completed related examinations.

The elderly people would be included in our study according to the following criteria: (1) being aged≥70 years; (2) being willing or able to complete the examinations and to meet the requirements of the study; (3) having no cerebral stroke history which would be further proved by brain CT or MRI scan and with their Hachinski Ischemic Score (HIS) score ≤4; (4) being free from non-AD dementia, such as Parkinson disease, frontotemporal dementia, normal pressure hydrocephalus, epilepsy, brain trauma, brain tumor, intracranial infection and others; (5) having no depression and with the Hamilton Rating Scale for Depression (HAMD) score <7; (6) having no other psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria; (7) having no drug or alcohol abuse and dependence in two years; (8) having no high level of blood glucose resisting treatment or control, or serious diabetic complications; (9) having no thyroid disease, vitamin B12 or folic acid deficiency; (10) having no other clinically significant and unstable medical illnesses.

Criteria for Hyperinsulinemia and Insulin Resistance

Venous blood of 2 mL was taken from elbow vein of each participant after 8-hour fast in the morning. Fasting blood glucose (FBG) was analyzed by the entire automatic biochemistry meter in the corresponding kit (Sigma Chemical Co, America). Fasting insulin (FINS) was analyzed with radioimmunoassay reagents (BNIBT Co, China).

Homeostasis model assessment (HOMA) has been used to predict the insulin sensitivity, which is calculated by the below formula: Homa IR=FPG× FINS/22.5, according to the one modified by Haffner in 1996[8].

The cutoffs for defining HI and IR in this study are as below. Participants who had a fasting insulin level (FINS) >10.5 mU/L were defined as having HI; otherwise they were included in the normal insulin level group with the insulin level ≤10.5 mU/L. Participants whose Homa IR>2.31 were defined as having IR; otherwise they were included in the non-IR group with Homa IR≤2.31. The cutoff of 10.5 mU/L for FINS accorded with the criterion of the endocrine laboratory in our hospital, and the cutoff of 2.31 for Homa IR followed the criterion in the report by Chen Lei[9].

Cognitive Testing

Trained research staff administered a battery of cognitive rating scales, including Mini-mental State Examination (MMSE)[10], Montreal Cognitive Assessment (MOCA)[11], Alzheimer Disease Assessment-cognition (ADAS-cog)[12], Clinical Dementia Rating (CDR)[13], Global Deteriorate Scale (GDS)[14], and Activities of Daily Living Scale (ADL)[10].

Global cognitive status was assessed by using MMSE and MOCA. MMSE (scored 0-30) is the most widely used test of cognitive functions. Its test items cover five different cognitive domains: orientation, immediate memory, delayed memory, attention/ calculation, and linguistic capacity. The five cognitive domains of each participant were analyzed in our study. MOCA was developed as a brief screening instrument for MCI and mild AD and was thought more sensitive than MMSE. MOCA has a maximum score of 30 points. The cognitive domains evaluated by MOCA are similar to those evaluated by MMSE. The ADAS-cog consists of twelve subscales that are designed to assess various cognitive abilities, including those associated with memory, language and praxis. A wrong response to each question of every item is recorded as scoring one point. The scores range from 0 to 75 and higher scores indicate greater cognitive recession. CDR is frequently used in trials. Six domains are assessed, that is: memory, orientation, judgment (problem solving and financial

affairs), community affairs (function at work, volunteer and social groups), home (function within home, hobbies), and personal care. CDR ratings are 0 for unimpaired people, 0.5 for questionable impairment, and 1, 2, or 3 for mild, moderate and severe dementia. In accordance with CDR, we differentiated participants by five stages, stage 1 for CDR 0 participants, and stage 2, 3, 4, or 5 for CDR 0.5, CDR 1, CDR 2, and CDR 3 participants respectively. GDS is made up of detailed clinical description of seven major distinguishable stages, ranging from normal cognition (1 score) to very severe dementia (7 scores). The clinician chooses the description which most closely matches the clinical state of a patient. According to GDS, the participants were divided into three groups, the normal group for GDS 1 and 2 participants, the cognitive dysfunction group for GDS 3, 4 and 5 participants, and the severe cognitive dysfunction group for GDS 6 and 7 participants. In addition, the 20-item ADL was administered to assess basic daily activities, like bathing, dressing and feeding. The response to each item on the ADL subscales is scored from 1 to 4, with 1 indicating "no difficulty at all", 2 "being able to do with some difficulty", 3 "needing help", and 4 "being unable to do". The scores on each of the items are added together to get the total item scores, which range from 20 to 80.

Statistical Analysis

All measurement data were expressed as mean±SD. All counting data were expressed as ratios and frequency. SPSS10.0 was used and results were considered statistically significant if $P<0.05$. *T*-tests were used to compare the measurement data. The ratios of count data were compared with χ^2 tests.

Partial correlation analyses were used to evaluate the relation of cognitive function with HI or IR. We conducted partial correlation analyses with two models, Model 1 adjusted for FBG and diabetes history and Model 2 adjusted for FBG, diabetes history, age, sex, education, smoking, hypertension, hyperlipemia, and coronary heart disease history.

RESULTS

Demographic Characteristics of the Study Population

Table 1 summarizes the characteristics of participants with different insulin levels and insulin sensitivity. Of the 328 participants in our study, 180 fulfilled the HI criterion (defined by FINS>10.5 mU/L). And the other 148 were classified as without HI. No differences were found between the groups with HI and without HI in the characteristics, such as age, sex, education and presence of hypertension, hyperlipidemia, and coronary heart disease history. But the elders with HI had higher levels of FBG and tended to be more likely to have a history of diabetes and smoking than those without HI.

Of the 328 participants in our study, 192 were classified as IR, according to the above criterion (defined by Homa IR>2.31). And the other 136 were included in the group without IR by the same criterion. Similar findings about the characteristics were observed when the elders with and without IR were compared, apart from the smoking history which showed no difference in the two groups (data shown in Table 1).

Table 1. Comparison of Characteristics between Subjects with and without HI or IR

Characteristics	Without HI (*n*=148)	With HI (*n*=180)	*P* Value	Without IR (*n*=136)	With IR (*n*=192)	*P* Value
Age (years)	79.39±5.56	79.66±5.79	0.6764	79.46±5.56	79.59±5.78	0.7513
Sex (male/female)	116/32	139/41	0.8940	106/30	148/44	0.8940
Education (years)	13.56±3.96	13.45±3.86	0.7913	13.53±3.88	13.49±3.93	0.9288
FBG (mmol/L)	5.28±1.43	5.85±1.78	0.0019**	5.13±1.25	6.07±1.96	<0.001**
Diabetes history (yes/no)	43/105	82/98	0.0030**	30/106	96/96	<0.001**
Smoking history (yes/no)	46/102	76/104	0.0400*	44/92	77/115	0.1650
Hypertension history (yes/no)	117/31	155/25	0.1050	107/29	164/28	0.1390
Hyperlipidemia history (yes/no)	54/94	71/109	0.6480	47/89	78/114	0.2990
Coronary heart disease history (yes/no)	89/59	111/69	0.8200	81/55	118/74	0.7320

Note. HI=hyperinsulinemia; IR=insulin resistance; FBG=fasting blood glucose; *$P<0.05$; **$P<0.01$.

Cognitive Functions

The elders with HI had lower cognitive scores than those without HI, evaluated by MMSE (*P*=0.0271) and MOCA (*P*=0.0162). More proportional participants in the group with HI belonged to Stage 3, 4, or 5 of CDR, compared to the group without HI (*P*=0.004). As far as GDS was concerned, such difference failed to reach statistical significance (*P*=0.179). While no significant differences were found in ADAS-cog or ADL scores between the two groups (Table 2).

The elders in the group with IR had worse cognitive functions than those in the group without IR, evaluated by MMSE (*P*=0.0312), MOCA (*P*=0.0287), CDR (*P*=0.018), and GDS (*P*=0.04). Nevertheless, no significant differences were found in ADAS-cog or ADL scores between the two groups.

Table 2. Comparison of Cognitive Scores between Subjects with and without HI or IR

Item	Without HI (*n*=148)	With HI (*n*=180)	*P* Value	Without IR (*n*=136)	With IR (*n*=192)	*P* Value
MMSE	26.31±4.43	25.09±5.32	0.0271*	26.40±4.40	25.25±4.97	0.0312*
MOCA	21.87±5.76	20.03±6.97	0.0162*	21.93±5.70	20.26±6.76	0.0287*
ADAS	15.35±13.15	16.19±12.67	0.6833	14.70±12.48	15.95±11.74	0.5198
ADL	25.96±10.90	27.99±10.17	0.0986	25.71±10.13	27.75±10.32	0.0856
CDR (*n*, %)			0.004**			0.018*
Stage 1	26 (17.6%)	24 (13.3%)		25 (18.4%)	25 (13%)	
Stage 2	100 (67.6%)	96 (53.3%)		90 (66.2%)	106 (55.2%)	
Stage 3	15 (10.1%)	35 (19.4%)		14 (10.3%)	36 (18.8%)	
Stage 4	5 (3.4%)	19 (10.6%)		5 (3.7%)	19 (9.9%)	
Stage 5	2 (1.4%)	6 (3.3%)		2 (1.5%)	6 (3.1%)	
GDS (*n*, %)			0.179			0.04*
Normal	81 (54.7%)	80 (44.4%)		78 (57.3%)	83 (43.2%)	
Cognitive dysfunction	65 (43.9%)	97 (53.9%)		56 (41.2%)	106 (55.2%)	
Severe cognitive dysfunction	2 (1.4%)	3 (1.7%)		2 (1.5%)	3 (1.6%)	

Note. HI=hyperinsulinemia; IR=insulin resistance; MMSE=mini-mental state examination; MOCA=Montreal cognitive assessment; ADAS-cog=Alzheimer disease assessment-cognition; ADL=activities of daily living scale; CDR=clinical dementia rating; GDS=global deteriorate scale; *P<0.05; **P<0.01.

We further analyzed MMSE scores by quartiles of insulin levels and Homa IR and found that cognitive scores decreased with the rise of insulin levels and IR for the third and fourth quartiles, which were statistically significant (P<0.05 or P<0.01) (Figure 1, 2).

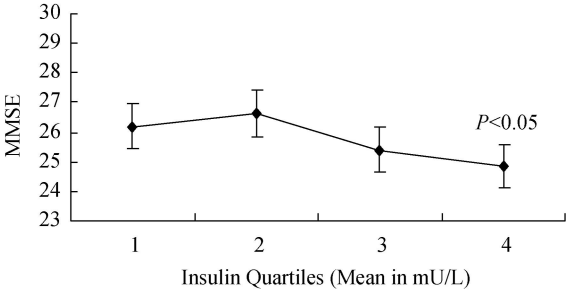

Figure 1. Change trend of MMSE scores in insulin quartiles.

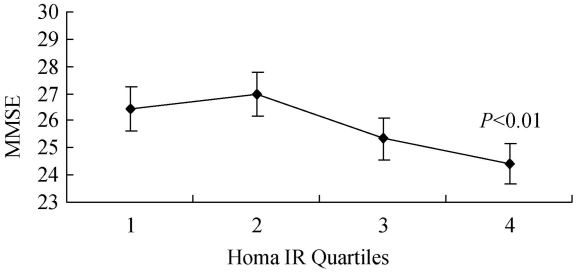

Figure 2. Change trend of MMSE scores in Homa IR quartiles.

Scores of Different Cognitive Domains

Scores of the five cognitive domains from MMSE were also compared between different groups with and without HI or IR. The group with HI showed lower scores in orientation (*P*=0.0079), delayed memory (*P*=0.0393), and attention/calculation

(*P*=0.0484) domains, whereas scores in the other two domains, immediate memory and linguistic capacity, did not differ between the two groups. The same differences were observed between the two groups with and without IR. The elders in the IR group had lower scores in orientation (*P*=0.0289), delayed memory (*P*=0.0457), and attention/ calculation (*P*=0.0495) domains (Table 3).

Table 3. Comparison of Scores of Different Cognitive Domains between Subjects with and without HI or IR

	Without HI (*n*=148)	With HI (*n*=180)	*P* Value	Without IR (*n*=136)	With IR (*n*=192)	*P* Value
Orientation	9.28±1.82	8.66±2.30	0.0079**	9.26±1.91	8.76±2.15	0.0289*
Immediate memory	2.88±0.49	2.85±0.49	0.6032	2.90±0.44	2.85±0.48	0.4039
Delayed memory	2.17±0.91	1.94±1.07	0.0393*	2.21±0.87	1.98±1.07	0.0457*
Attention/calculation	3.91±1.34	3.58±1.68	0.0484**	3.93±1.34	3.60±1.64	0.0495*
Linguistic capacity	8.18±1.27	8.02±1.22	0.2300	8.18±1.22	8.07±1.12	0.4293

Note. HI=hyperinsulinemia; IR=insulin resistance; *P<0.05; **P<0.01.

The Correlation Analyses between Cognitive Functions and Insulin Levels or Homa IR

Partial correlation analyses were conducted by two models. Model 1, adjusted for FBG and diabetes history, demonstrated that the insulin levels had negative correlation with the scores of MMSE (*r*=-0.204, *P*<0.001) and delayed memory (*r*=-0.241, *P*<0.001). The Homa IR also had negative correlation with the scores of MMSE (*r*=-0.231, *P*<0.001), orientation (*r*=-0.118, *P*=0.037), delayed memory (*r*=-0.261, *P*<0.001), and attention/calculation domains (*r*=-0.143, *P*=0.012).

Following adjustment for FBG, diabetes history, age, sex, education, smoking, hypertension, hyperlipemia and coronary heart disease history, the partial correlation analyses by model 2 exhibited similar correlation. The insulin levels had negative correlation with the scores of MMSE (*r*=-0.185, *P*=0.001) and delayed memory (*r*=-0.230, *P*<0.001). The Homa IR had negative correlation with the scores of MMSE (*r*=-0.226, *P*<0.001), delayed memory (*r*=-0.263, *P*<0.001), orientation (*r*=-0.120, *P*=0.034), and attention/calculation domains (*r*=-0.131, *P*=0.023) (Table 4).

Table 4. Correlation Analyses between Cognitive Functions and Insulin Levels or Homa IR

	Model 1				Model 2			
	FINS	*P* Value	Homa IR	*P* Value	FINS	*P* Value	Homa IR	*P* Value
MMSE	-0.204	<0.001**	-0.231	<0.001**	-0.185	0.001**	-0.226	<0.001**
Orientation	-0.101	0.082	-0.118	0.037*	-0.088	0.127	-0.120	0.034*
Immediate memory	-0.096	0.092	-0.082	0.149	-0.066	0.254	-0.058	0.318
Delayed memory	-0.241	<0.001**	-0.261	<0.001**	-0.230	<0.001**	-0.263	<0.001**
Attention/calculation	-0.106	0.063	-0.143	0.012*	-0.086	0.139	0.131	0.023*
Linguistic capacity	-0.089	0.119	-0.110	0.053	-0.078	0.178	-0.105	0.069

Note. MMSE=mini-mental state examination; FINS=fasting insulin; Homa IR=Homeostasis model assessment of insulin resistance; The model 1 was adjusted for FBG and diabetes; The model 2 was adjusted for diabetes, age, sex, education, smoking, hypertension, hyperlipemia, and coronary heart disease; *P<0.05; **P<0.01.

DISCUSSION

Abnormalities in insulin metabolism are major characteristics of type 2 diabetes in the older cohort. Reduced sensitivity of insulin receptors to insulin is known as IR, and it results in an elevated level of insulin by feedback, termed HI. Chronic HI and IR are thought to influence the onset of a number of metabolic related diseases. In the past, it was believed that insulin could not cross the blood-brain barrier (BBB), and had no effect on the central nervous system (CNS). However, in the latest 30 years, there has been solid evidence that insulin and insulin receptors are present and play many roles in CNS. Some studies reported that neuronal survival, metabolism, outgrowth, and plasticity are all directly

modulated by insulin, and that it is an important nerve nutrition hormone. These modulations are closely related to cognitive functions, such as learning and memory domains. A recent study demonstrated that insulin had a cognition-enhancing effect on patients with Alzheimer disease (AD)[15-16]. On the contrary, there are also conflicting data relating IR and HI to cognitive decline and AD. A longitudinal study that enrolled 2 322 participants and had been followed up for 32 years reported that impaired insulin response at midlife was associated with an increased risk of AD, suggesting a causal link between insulin metabolism and pathogenesis of AD[17]. A study with a large sample of older women without diabetes found that those in the group with high levels of insulin secretion had obvious decline in global cognition and verbal memory up to 10 years later, in comparison to those with lower levels of insulin secretion[18]. Isik studied the possible relation between IR and cognitive statuses of the elderly regarding normal and mild cognitive impairment (MCI) and AD. There were no statistically significant differences in Homa IR and quantitative insulin sensitivity check index (QUICKI) scores among all the groups[19].

To observe the relationship between cognitive functions of the elders and HI or IR, this study included 328 older participants, and their FINS, FBG, Homa IR and cognitive functions were examined. Some general characteristics of the participants require some explanation. The elders with HI or IR tended to be more likely to have a history of diabetes than those without HI or IR. But no differences were found between the groups in the presence of hypertension, hyperlipidemia, coronary heart disease, which was contradictory to the current knowledge about metabolic syndrome. A possible reason for this contradiction was that the participants enrolled in our study were very old and the incidences of hypertension and hyperlipidemia at their ages were so high that it was difficult to find the difference between groups. Another possibility was that it could be just due to chance.

The participants were divided into different groups, the groups with and without HI or the groups with and without IR. The HI criterion was defined by FINS>10.5 mU/L, and the IR criterion was defined by Homa IR>2.31. The study showed that the scores of MMSE and MOCA in the groups with HI or IR were lower, as compared with those in the groups without HI or IR. Moreover, the ratios of the patients suffered from impaired cognitive functions were higher in the groups with HI or IR than the groups without HI or IR. These results indicated that the elderly with abnormal insulin metabolism had worse general cognition. The relations between insulin metabolism and cognitive functions were well displayed by our correlation analyses. No matter whether or not the correlation models were adjusted for FBG, diabetes or other global characteristics, a negative correlation was still statistically significant between MMSE scores and FINS, as well as between MMSE scores and Home IR.

The trends of cognitive functions, following increase of insulin levels and IR, were shown by quartile trend figures. The participants in our study were divided into quartile groups. The mean MMSE scores of each quartile group were calculated to obtain the trend figures. The figures showed that the MMSE scores decreased with the increase of insulin levels and IR. The cognitive decline began from the third quartiles and lower scores were observed in the fourth quartiles.

In our study, MMSE scores of the older participants came from five cognitive domains: orientation, immediate memory, delayed memory, attention/ calculation and linguistic capacity. The elders with HI or IR showed lower scores in orientation, delayed memory and attention/calculation domains than those without HI or IR. But the differences in the immediate memory and linguistic capacity between different groups were not statistically significant. In addition, negative correlations of delayed memory with insulin levels and Homa IR were always observed in two adjusted models of partial correlation analysis. Our findings were consistent with several other reports[20-22].

Taken together, a normal insulin level is necessary for cognitive functions. With increase of IR, chronic HI was a risk factor for cognitive decline of the elders. High insulin levels and IR may affect the brain and cognition through several mechanisms, some of which are still unclear. Firstly, the chronic HI and IR result in accumulation of advanced glycosylated end products (AGES). AGES can aggravate the oxidative stress of the central nervous system, which is known to contribute to cognitive disorders[19]. Secondly, insulin and amyloid beta (Aβ), the main product of senile plaque (SP), are both substrates of the insulin degrading enzyme (IDE). IDE in the brain is a regulator of extracellular Aβ level. Insulin at an increased level can inhibit the degradation of Aβ by competitive inhibition of IDE in the brain, thus increasing its deposition in plaques[19,23-24]. Thirdly,

some studies have proved that HI also plays a role in the promotion of phosphorylation of tau protein, the main component of neurofibrillary tangles (NFTs)[19,24]. In addition, there are several other possible mechanisms related to insulin metabolic disorder that may be also related to impaired cognitive functions, e.g. diffusely cerebral microvascular disease and abnormal signal transduction pathways downstream of insulin.

In a word, this study demonstrates that HI and IR are important risk factors for cognitive decline of the elders. The dysfunctions in orientation, delayed memory, and attention/calculation have been observed. Considering the above results, we should take effective preventive measures to reduce the prevalence of senile dementia and delay the course of diseases. To overcome central nervous IR and enhance central nervous insulin signaling by pharmacological interventions, for example insulin analogues or insulin sensitizers, will be an attractive strategy in future clinical practices[25].

There are several limitations in our study that may limit the interpretation of the results. Owing to advanced ages of the participants, determination of insulin levels and IR statuses in cerebrospinal fluid as a traumatic examination was not done in this study. Therefore, we do not know if our findings on peripheral abnormal insulin metabolism can apply to the central status. Further studies on the association of central insulin metabolism with dementia are necessary. As this study just began two years ago, we are unable to quantify the cognitive function change of individuals by the longitudinal statistical analyses. Another study should be followed to observe the cognitive decline of those older people categorized according to different forms of insulin metabolism.

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