Patients with both cognitive impairment and solid cancer present increased insulin resistance

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Research note

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Abstract

Objective In an aging population, an increase in elderly cancer patients with cognitive impairment is to be expected. Because cognitive impairment has a serious impact on quality of life of cancer patients, it is important to elucidate the possible association between cancer and cognitive impairment. Here, we focused on glucose metabolism as a factor that links cancer and cognitive impairment.

Results A homeostasis model assessment was used to assess insulin resistance (HOMA-IR) and \( \beta \)-cell function (HOMA-B). HOMA-B showed no difference among patients with cancer, with dementia, and with both. However, there was a significant difference in HOMA-IR. In comparison with patients with only solid cancer, patients with only cognitive impairment and those with both cancer and cognitive impairment showed increased HOMA-IR value. Insulin resistance was increased in patients with cognitive impairment only and those with both cognitive impairment and solid cancer compared to cancer patients without cognitive impairment; however, \( \beta \)-cell function was not affected. The present data indicate that elderly cancer patients with a high HOMA-IR score may be in higher risk of developing cognitive impairment. Furthermore, early treatment to reduce insulin sensitivity may become the prevention of cognitive impairment.

Background

An increase in elderly patients with cancer, cognitive impairment or both, is inevitable in an aging population. It has recently been shown that up to 30% of patients with cancer exhibit cognitive impairment [1-5], which can have a serious impact on quality of life for both patients and families. However, the association between cognitive impairment and cancer remains unknown, and there is no effective treatment for such patients. Recent studies have indicated that diabetes contributes to the development of cognitive impairment such as Alzheimer’s disease [6]. A number of reports have also indicated that hyperglycaemia is a contributing factor to the progression of cancer [7]. Therefore, hyperglycaemia or glucose intolerance may be the key factor that links the development of cognitive impairment and cancer [8]. Hyperglycaemia can be induced by two different mechanisms. One is the reduction of insulin secretion from pancreatic \( \beta \)-cells and another is the increase in insulin resistance in target organs. It is well known that the majority of diabetes cases in Asia are caused by reduction of insulin secretion; whereas, those in the US and Europe are due to insulin resistance. However, little is known regarding the contribution of hyperglycaemia to cognitive impairment and cancer. As the number of elderly cancer patients with cognitive impairment is expected to increase, it is important to understand the underlying mechanism that links both diseases. In this study, we focused on the aspect in which hyperglycemia may link cognitive impairment and cancer. We applied a homeostasis model assessment (HOMA) to assess insulin resistance (HOMA-IR) and \( \beta \)-cell function (HOMA-B) in elderly patients with solid cancer (patients with cancers of the esophagus, gastric area, colon, bile duct, prostate, mammalian, lung and ovary) and those with cognitive impairment, as well as in patients with both cancer and cognitive impairment.
Methods

Patient information

Thirteen subjects (7 males and 6 females, with average age of 85) with solid cancers and cognitive impairment were recruited (Table). As a control, 14 subjects (6 males, 8 females, with average age of 86) with only cognitive impairment were recruited and 8 subjects (5 males, 3 females, with average age of 88) with only cancer were recruited.

Research methods

For cognitive assessments, the patients underwent both Mini-Mental State Examination (MMSE) [9-11] and Revised Hasegawa's dementia scale (HDS-R) tests [12]. Eight subjects (5 males, 3 females, with average age of 88) with cancer only were recruited. Blood samples were collected at 07:00 A.M. after overnight fasting to measure fasting plasma glucose and fasting insulin levels.

Statistical analysis

A homeostasis model assessment (HOMA) was used to assess insulin resistance (HOMA-IR) and \( \beta \)-cell function (HOMA-B). These values were calculated by using a HOMA calculator available on the Diabetes Trials Unit website (http://www.dtu.ox.ac.uk). All the values are expressed as average +SD. Statistical analysis was made by a Student's t-test. Statistical Product and Service Solutions (SPSS Inc., Chicago, IL, USA) 20.0 software was used for statistical analysis. A \( P< 0.05 \) indicated a statistically significant difference.

Results

Comparison of \( \beta \)-cell function

When evaluating by HOMA-B, patients with cognitive impairment, with cancer and with both showed no significant difference (patients with cognitive impairment: 47.729±41.517%, cancer: 32.325±30.834%, both: 29.877±19.801%) (Fig. A).

Comparison of insulin resistance

Insulin resistance assessed by HOMA-IR showed a significant difference among the groups. HOMA-IR was significantly increased in patients with cognitive impairment only (1.307±0.673) and those with both cognitive impairment and cancer (1.896±0.435), compared to patients with only cancer (0.645±0.196) (Fig. B).

Clinical features of the patients and the relationship between BS and IRI level

Blood sugar (BS) and immunoreactive insulin (IRI) levels of patients with both cognitive impairment and cancer are higher than those of patients with cognitive impairment only (\( P < 0.05 \)) (Table).
Discussion

In the present study, we have shown that insulin resistance (as assessed by HOMA-IR) is increased in patients with cognitive impairment regardless of the presence of solid cancer, compared to that in cancer patients without cognitive impairment. HOMA-IR showed no significant differences between patients with cognitive impairment only and those with both cognitive impairment and cancer, therefore it is possible to consider that the existence of solid cancer itself may have no contribution to the development of insulin resistance in cancer patients.

To date, there have been many studies indicating the relationship between insulin resistance and development/progression of cancer [13]. However, in the present study, HOMA-IR of patients with cancer only was significantly lower compared to those with cognitive impairment only. Therefore, the contribution of insulin resistance to the development and progression of cancer was not indicated and further studies are required. On the other hand, recent epidemiological and basic scientific investigations have suggested an association and common pathological mechanisms between hyperglycaemia and cognitive impairment including Alzheimer's disease [7]. As for the mechanisms for the development of cognitive impairment in diabetic patients, interference of insulin signal processing in the brain has been indicated. Wan et al. reported that insulin induces functional postsynaptic GABA receptors in the brain [14]. Furthermore, low insulin sensitivity is reported to contribute to the decrease in acetylcholine synthesis, which leads to Alzheimer's disease [15]. Our present data confirms that cancer patients are no exception to develop hyperglycaemia due to low insulin sensitivity which induces cognitive impairment. However, because HOMA-IR showed no significant difference between patients with cognitive impairment only and patients with both cancer and cognitive impairment, insulin resistance may not contribute solely to the development of cognitive impairment in patients with solid cancers. Interestingly, the majority of Japanese diabetic patients are known to have insulin secretion deficiency but not insulin resistance [16]. Our present data may also indicate the importance of HOMA-IR measurement in elderly cancer patients since those with high HOMA-IR scores may be in higher risk of developing cognitive impairment. Early treatment to reduce insulin sensitivity, such as with the use of biganides, in patients with high HOMA-IR scores, is important. However, further studies are required to investigate the effects of biganides on the development of cognitive impairment in elderly cancer patients.

Conclusions

In summary, our results suggest that insulin resistance was increased in patients with cognitive impairment only and those with both cognitive impairment and solid cancer compared to cancer patients without cognitive impairment; however, β-cell function was not affected. The present data indicate that elderly cancer patients with insulin resistance may be in higher risk of developing cognitive impairment. Early treatment to reduce insulin sensitivity may be able to the prevention of cognitive impairment.

Limitations
The study cannot show cause-effect relationship. Social desirability and recall bias were also possible limitations.

**Abbreviations**

HOMA-IR: homeostasis model assessment was used to assess insulin resistance

HOMA-B: homeostasis model assessment was used to assess β-cell function

BS: Blood sugar

IRI: immunoreactive insulin

**Declarations**

**Ethics approval and consent to participate**

The Institutional Review Board (IRB) at the local Ethics Committee (the Ethical Review Board of Japan Community Healthcare Organization Nihonmatsu Hospital (no. 00037)) approved the study. All followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation in Fukushima Medical University and with the Helsinki Declaration of 1975, as revised in 2000. Each author certifies that all investigations were conducted in conformity with the ethical principles.

MMSE average score of thirteen subjects with solid cancers and cognitive impairment was 22.6, and 14 subjects with only cognitive impairment was 21.4. The score of the MMSE study of the patients are 23 points or less. It may be said that the patients are cognitive decline. We reviewed the consent form that submitted to the Ethical Review Board in reference to the background and the design of the LASA study. I obtained the qualification of the specialist in intractable disease designation from Governor Fukushima. For example, an intractable disease is frontal head form dementia or young people dementia appointed by Japanese Ministry of Health, Labor and Welfare. Written informed consent was obtained from the legal guardians or representative of thirteen subjects with solid cancers and cognitive impairment and 14 subjects with only cognitive impairment these participants provided consent on their behalf included in the study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The dataset in the current study is available from the corresponding author upon request.

**Competing interests**
The authors declare that they have no financial or non-financial competing interests.

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**Authors’ contributions**

KG, KY and YR performed patient recruitment and clinical investigation. KG, KY, YR, SH, YM and KS conceived of the study, participated in its design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

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Tables

The clinical features and level of patients with both cognitive impairment and cancer

| age | gender | cognitive impairment | cancer | BS  | IRI | IR  | %B |
|-----|--------|----------------------|--------|-----|-----|-----|-----|
| 87  | M      | Alzheimer            | esophagus | 204 | 6.1 | 0.95| 16.5|
| 88  | M      | Alzheimer            | Stomach  | 192 | 11.6| 1.77| 30  |
| 88  | F      | Cerebrovascular      | Stomach  | 213 | 12.2| 1.91| 26  |
| 79  | F      | Cerebrovascular      | Colon    | 190 | 11.9| 1.81| 31.1|
| 91  | M      | Cerebrovascular      | Colon    | 273 | 10.4| 1.91| 15.1|
| 80  | M      | Alzheimer            | Colon    | 195 | 8.5 | 1.31| 23  |
| 85  | F      | Alzheimer            | pancreas | 318 | 10.3| 2.38| 11.8|
| 81  | M      | Alzheimer            | bile duct| 191 | 11.2| 1.71| 29.4|
| 91  | M      | Cerebrovascular      | prostate | 220 | 13.3| 2.1 | 26.3|
| 78  | F      | Alzheimer            | Breast   | 110 | 12.7| 1.72| 90.4|
| 94  | M      | Alzheimer            | lung     | 198 | 16.3| 2.48| 37  |
| 80  | F      | Parkinson            | ovary    | 200 | 15.4| 2.35| 34.8|
| 78  | F      | Alzheimer            | Vulvar   | 275 | 12.2| 2.25| 17  |

BS: blood sugar (mg/dl), IRI: insulin (µU/mL), IR: insulin resistance (HOMA-IR), %B: β-cell function (HOMA-B) (%)
Figure 1

Results of HOMA-B evaluation HOMA-B of patients with cancer, with cognitive impairment, and with both showed no significant difference. Data represent mean ± SD. P values determined using Student's t test. *, P ≤ 0.001; **, P ≤ 0.05.
Figure 2

Results of HOMA-IR evaluation HOMA-IR was significantly increased in patients with cognitive impairment only and those with both cognitive impairment and cancer compared to patients with only cancer. Data represent mean ± SD. P values determined using Student's t test. *, P ≤ 0.001; **, P ≤ 0.05.