1. **No.**

   FP01811128

2. **Title**

   Impact of Smoking on Cerebrovascular Diseases and Cognitiv Inpairament in Patinets with Diabetes and/or Obesity: Pathophysiological Significance of Monocyte Function anf TREM2

3. **Period**

   2018-2018

4. **Summary**

   The aim of the present study is to elucidate the effects of smoking on cognitive impairment in Japanese patients with type 2 diabetes and/or obesity, by focusing on the M1/M2 axis and the levels of TREM2. We performed clinical studies in a cross-sectional approach, using a database of a prospective cohort comprising Japanese patients with type 2 diabetes and/or obesity, to examine the effects of smoking on MMSE scores and the relationships between those effects, M1/M2 axis, and TREM2 levels. Basic studies were also performed; we investigated the effects of diabetes/obesity on M1/M2 axis and TREM2 levels, using a mouse model of dementia and a mouse microglial cell line.

   We analyzed 670 patients. The serum levels of soluble TREM2 (sTREM2) showed a significant positive association with an increased risk of cognitive impairment (MMSE $\leq$ 26); however, there were no significant relationships between smoking, serum levels of sTREM2, and MMSE, after adjusting for confounding factors. We observed significant increases in the hippocampal expression levels of TREM2 and the systemic levels of inflammation, in a mouse model of dementia fed high-fat diet compared to standard diet. A microglial cell line produced proinflammatory cytokines and elevated TREM2 expression levels, in response to stimulation with saturated fatty acid (palmitic acid).

   In this cross-sectional analysis of clinical studies, in Japanese patients with type 2 diabetes and/or obesity, the association between smoking and cognitive decline was not significant. Conversely, our basic studies revealed the deleterious effects of diabetes/obesity on the exacerbation of inflammation in the brain.