The dual impact of homocysteine and cholesterol on cognitive functions

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Background
There is some debate about the role of cholesterol in cognitive functions. Cholesterol has been accused of its deleterious effect on cognitive functions since decades. Others talked about its beneficial outcomes on cognition.

Aim
The aim of the study was to find the correlation between total cholesterol (TC) and cognitive functions and if it is homocysteine (Hcy) dependent.

Participant and methods
We enrolled 41 individuals, aged 55 years old and over. All participants underwent measurement of serum Hcy and TC and other lipid profile components. Assessment of cognitive functions was done by two batteries: Mini-Mental State Exam (MMSE) and Memory Assessment Scale (MAS).

Results
Forty participants were found to have normal Hcy levels (2.499 ± 0.77 μmol/l). According to the TC level, the participants were divided into three tertiles, in those with the highest TC (>181 mg/dl) there was a direct significant correlation between TC and cgnitive functions as follows: MMSE ($P = 0.01$), total MAS score ($P = 0.04$), verbal memory ($P = 0.01$), and visual memory ($P = 0.03$). Also, it was noticed that MMSE ($P = 0.03$), total MAS ($P = 0.03$), verbal memory ($P = 0.04$), and visual memory ($P = 0.02$) had significant positive correlations with high-density lipoprotein cholesterol. Also, MMSE ($r = 59$, $P = 0.00$) and total MAS ($r = –0.39$, $P = 0.01$) had significant negative correlation with low-density lipoprotein cholesterol.

Conclusion
High serum TC levels, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol may have protective effects on cognitive functions. However, the authors could not confirm if there is a dual correlation between serum TC and Hcy levels on cognitive functions, as all the participants had normal Hcy levels.

Keywords:
cholesterol, cognitive functions, homocysteine, lipid profile, memory assessment scale, mini mental state exam

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Introduction

Dementia is more common in the elderly; it is not a normal part of the aging process [1].

The relationship between serum total cholesterol (TC) levels and cognitive functions remains wily. Some studies have suggested that elevated TC in old participants is associated with a decreased risk of dementia [2]. Others had indicated that elevated TC may be a risk factor for cognitive decline and Alzheimer's disease [3]. However, a recent study published by Cheng *et al*. [4] showed that the lowest (≤125.26 mg/dl) and highest (>186.73 mg/dl) TC groups were associated with lower cognitive scores in the presence of normal homocysteine (Hcy).

Neurons are in need of continuous supplementation of cholesterol to maintain their constant concentration in plasma membranes and reserve their integrity [5].

On the other hand, elevated TC can lead to a compromised vasculature and reduced cerebral perfusion, which will lead to structural microvascular modulation and change of the blood–brain barrier ending in the formation of plaques and death of neurons [6].

The hazardous effects of elevated Hcy on cognition may be through its action as an excitatory neurotransmitter by competing with inhibitory neurotransmitters such as gamma-aminobutyric acid, through increasing vascular permeability by acting as an excitatory neurotransmitter [7,8].

Aim

The aim was to find the correlation between TC and cognitive function and if it is Hcy dependent.

Participants and methods

This study was conducted on 41 healthy participants recruited from the outpatient clinic of Neurology Department in Assiut University Hospital from 1 January, 2018 to 31 June 2018. These participants who met the following inclusion criteria were included in this study: apparently healthy participants, who were aged 55 years and over, are still functioning, with normal or corrected vision adequate for normal reading as well as with normal or corrected hearing adequate for normal conversation.

Any participant who met these below-mentioned criteria was excluded from the start: first, any known patients diagnosed with dementia or other cognitive disorders, or other neurodegenerative diseases (Parkinson's, Huntington's, chorea, etc. cerebrovascular stroke, demyelinating diseases, psychiatric illness, renal and/or hepatic impairment, or thyroid dysfunctions or epilepsy or substance abuse. Second, compliant patients on statin pharmacotherapy, antiepileptic drugs, psychotropic drugs, or tranquilizers.

Ethical considerations

The study was approved by the Ethics Committee in the Faculty of Medicine, Assiut University (Approval Number: 17100550). The participants were informed about the nature and steps of the study and consent was obtained from each participant in the study.

Participants were subjected to the following:

(1) Full history taking
(2) Full general and neurological examination
(3) Laboratory investigations:
    After an overnight fast (10–12 h), venous blood sample (about 8 ml) was collected from each participant into two yellow- top (gel serum separator) vacutainer tubes. Blood was allowed to clot in tubes; sera were obtained by centrifugation. Sera were inspected to ensure it is not hemolyzed and were transferred into new tubes. Sera were used immediately (lipid profile) and divided into aliquots to be stored at −20°C till the time of Hcy assay
    TC, triglycerides (TGs), and high-density lipoprotein-cholesterol (HDL-C) were measured using CHOL_2 reagent (REF-10376501), TRIG_2 reagent (REF-10335892), and D-HDL reagent (REF-07511947), respectively, on Advia 1800 automated chemistry system (Siemens, Henkestr, Germany). Low-density lipoprotein (LDL-C) was calculated according to Friedewald calculation:

$$\text{LDL - C} = \text{Total cholesterol} - \left(\frac{\text{triglycerides}}{5 + \text{HDL - C}} \right)$$

    However, the accepted limit for this equation is a TG level of 400 mg/dl [9]
    Hcy was measured by enzyme-linked immunosorbent assay (ELISA) technique using Human Homocysteine ELISA Kit (catalog no. SG-10387; SinoGeneClon Biotech Co. Ltd, Hangzhou, China) and Stat Fax 2100 microplate reader (Awareness Technology Inc., USA).
(4) Cognitive function assessment:
    Interviews of cognitive assessment were conducted by a qualified psychologist, using previously standardized, validated, and reliable Arabic version of two cognitive assessment tests: Mini-Mental State Exam (MMSE) and Memory Assessment Scale (MAS). The time used for both tests was about 20–30 min:
    (a) MMSE, brief version: MMSE was the most commonly used screening test for cognitive decline. MMSE includes 11 items covering a person's orientation to time, place, recall ability, short-term memory, and arithmetic ability [10]
    (b) MAS assesses three areas of cognitive function which are critical in the assessment of memory: attention, concentration, and short-term memory; learning and immediate memory; and memory following a delay [11].

Statistical analysis

Data was collected and were analyzed using SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data was expressed in the form of mean ± SD or median (range), while nominal data was expressed in the form of frequency (percentage). We performed the test of normality (Shapiro test) and it was insignificant ($P > 0.05$). So we used parametric tests included Pearson's correlation. We subdivided the participants based on tertiles of cholesterol, first (<135 mg/dl), second (135–181 mg/dl), and third (>181 mg/dl). *P* value was significant if less than 0.05.

Results

Participants ($n = 41$) completed the cognitive assessment and one participant is excluded due to high abnormal Hcy level, 14.3 μmol/l (high normal 5.811.9 μmol/l, according to age and sex) [12]. In Table 1, we present data on the participant's demographic characteristics and their medical history. The number of illiterate to literate people was 30:10.

In Table 2, we displayed data on cognitive tests, MMSE and total MAS and MAS sub-domains. The MMSE cutoff point is 21 points for illiterate participants [13].

In Fig. 1, we present the data of lipid profile components. Mean level of Hcy is 2.499 ± 0.77 μmol/l. Table 3 shows participants' numbers according to their TC levels. Of all biomarkers considered in univariate models, TC, LDL-C, and HDL-C levels were significantly related to cognitive scores ($P < 0.05$). TG and Hcy were nonsignificantly associated with cognitive function.

Participants were divided into three tertiles based on the serum TC (Table 3) [14].

Table 1 Demographic data of the studied participants

Variables	*n*=40 [*n* (%)]
Age (years)	60.85±3.74 (55-72)
Sex	
Male	11 (25)
Female	30 (75)
Residence	
Rural	25 (62.5)
Urban	16 (37.5)
Diabetes mellitus	7 (17.5)
Hypertension	8 (20)
Other morbidities	
Ischemic heart disease	2 (5)
Bronchial asthma	1 (2.5)
Unilateral hearing loss	1 (2.5)
Facial palsy	1 (2.5)
Smoking	6 (15)
Years of education	5.25±2.97

Data was expressed in the form of frequency (percentage), mean (SD), or median (range).

Table 2 Mean of Mini-Mental State Exam and Memory Assessment Scale

	n=40
MMSE	22.13±1.94
Total MAS score	67.22±8.71
Short memory	66.22±10.20
Verbal memory	72.85±9.65
Visual memory	68.25±9.01

Data was expressed in the form of mean and SD. MAS, Memory Assessment Scale; MMSE, Mini-Mental State Exam.

Table 3 Correlation between different cognitive scores and cholesterol level

	Cholesterol level (mg/dl)					
	<135		135-181		>181	
	r	*P*	*r*	*P*	*r*	*P*
MMSE	0.40	0.40	0.09	0.98	0.39	**0.01**
MAS total score	0.15	0.53	0.50	0.13	0.30	**0.04**
Short memory	0.09	0.68	0.34	0.35	0.61	0.06
Verbal memory	0.14	0.55	0.37	0.29	0.40	**0.01**
Visual memory	0.05	0.83	0.47	0.16	0.61	**0.03**

MAS, Memory Assessment Scale; MMSE, Mini-Mental State Exam; Bold values: *P* significant if <0.05.

We found that there was a direct significant correlation between TC level in the third tertile and MMSE ($r = 0.39$, $P = 0.01$). The same result is observed with total MAS score ($r = 0.30$, $P = 0.04$) and its sub-domains: verbal memory ($r = 0.40$, $P = 0.01$) and visual memory ($r = 0.61$, $P = 0.03$).

On the other hand, in those with first tertile (TC <135 mg/dl) and second tertile (TC: 135–181 mg/dl), all cognitive scores had insignificant correlation with TC ($P > 0.05$).

Participant's numbers in each tertile are mentioned in Table 4, the sum of first and second tertile and the third tertile. In the third tertile, we found that eight participants are in the recommended international limits of normal TC (<200 mg/dl) and 12 participants had hypercholesterolemia (≥200 mg/dl) [15].

We searched for the relation of other lipid profile components and cognitive functions in the 40 participants. It was noticed that HDL-C had significant positive correlations with MMSE ($r = 0.29$, $P = 0.03$), total MAS score ($r = 0.34$, $P = 0.03$), verbal memory ($r = 0.33$, $P = 0.04$), and visual memory ($r = 0.36$, $P = 0.02$) (Figs. 2–5).

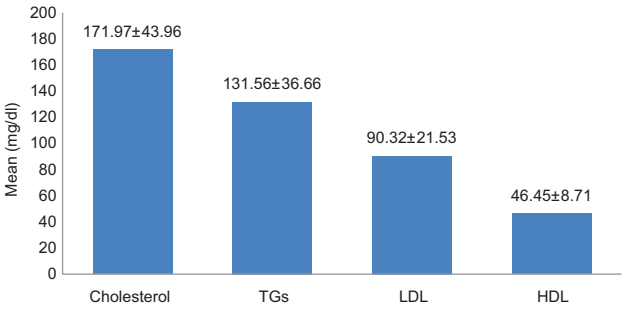
Also, it was noticed that LDL-C had significant negative correlation with MMSE ($r = -0.59$, $P = 0.00$) and total MAS score ($r = -0.39$, $P = 0.01$), but it had insignificant correlation with short memory, verbal memory, and visual memory (Table 5). TG was not significantly associated with cognitive function.

Discussion

Of the studies focusing on TC alone, conflicting results have been reported on the relationship between TC and cognitive functions.

In our study, we were guided by the Chinese study carried out by Cheng *et al.* [4], to find if there is a

Figure 1



Mean level of all lipid profile components.

Table 4 Distribution of participant's numbers based on total cholesterol level

Cholesterol level	*n*=40
First and second tertiles	
≤181 mg/dl	20 (50)
Third tertile	
181-200 mg/dl	8 (20)
≥200 mg/dl	12 (30)

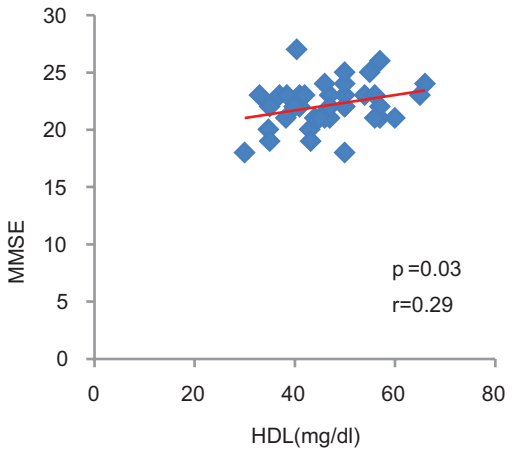
Data was expressed in the form of frequency (percentage).

Table 5 Correlation between different cognitive scores and low-density lipoprotein cholesterol

	Low density lipoprotein level	
	r	*P*
MMSE	−0.59	**0.00**
MAS total cognitive score	−0.39	**0.01**
Short memory	−0.30	0.56
Verbal memory	−0.23	0.14
Visual memory	−0.43	0.05

MAS, Memory Assessment Scale; MMSE, Mini-Mental State Exam; Bold values: *P* significant if <0.05.

Figure 2



Correlation between high-density lipoprotein cholesterol and Mini-Mental State Exam.

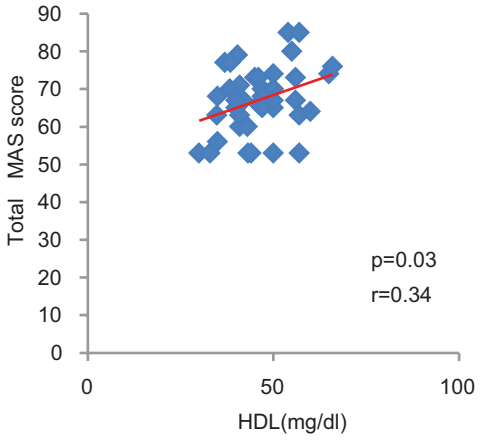
relation between TC and cognitive performance in the presence of Hcy. However, they found in their study that the lowest (≤125.26 mg/dl) and highest (>186.73 mg/dl) TC groups associated with bad cognitive function in normal Hcy levels were against our one. In this cross-sectional study of apparently nondemented participants, we observed an association between highest TC levels, HDL-C and LDL-C, and a decreased risk of cognitive dysfunction in the presence of normal Hcy level.

Total cholesterol and cognitive functions

There is growing evidence that higher Hcy levels are involved in age-related cognitive decline and various types of central nervous system disorders [16].

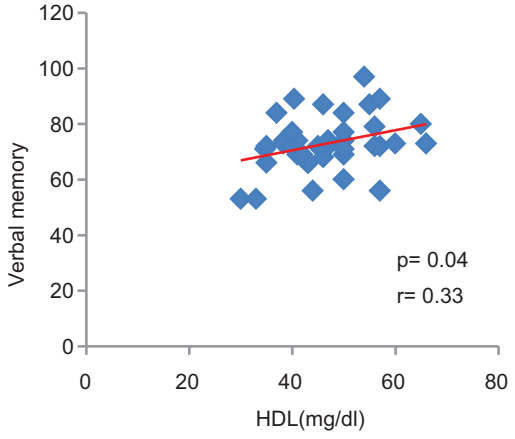
Fortunately, normal Hcy levels gave us the chance to study the clear relation between cholesterol, and

Figure 3



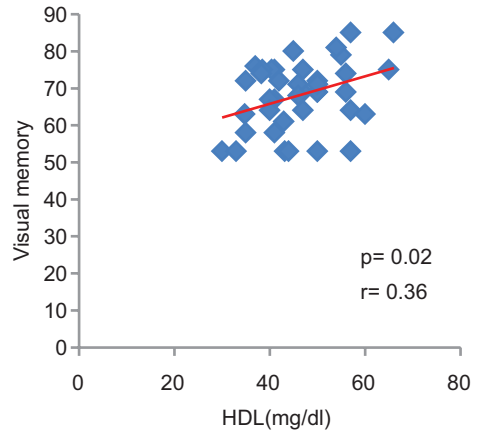
Correlation between high-density lipoprotein cholesterol total Memory Assessment Scale score.

Figure 4



Correlation between high-density lipoprotein cholesterol and verbal memory.

Figure 5



Correlation between high-density lipoprotein cholesterol and visual memory.

even other components of lipid profile, and cognitive functions in the old population. But unfortunately, we could not find out if the relation between TC and cognitive function is Hcy dependent.

In studies measuring cholesterol in old people, a high TC group was reported to be associated with cognitive impairment [17]. Others found that the lowest TC group was associated with cognitive decline [18], although few studies have reported no association between TC and dementia [19].

Examination of cholesterol in tertiles showed that the reduction in risk of cognitive decline was associated exclusively with the highest tertile (TC >181 mg/dl) and there was no relation between those with lowest TC and cognitive function (TC ≤181 mg/dl).

So, our data is against what Cheng *et al*. [4] observed, where participants with normal Hcy levels have an inverse U-shaped relationship between TC levels and cognitive score, indicating that both lowest (<125.26 mg/dl) and highest (>186.73 mg/dl) cholesterol levels were associated with bad cognitive scores.

However, in our study, some of these participants (20%) in the third tertile fall in the normal range of TC (<200 mg/dl) (Table 4), the cutoff point of hyperlipidemia [15]. They perform better than those in the first and second tertiles (≤181 mg/dl), which is also against the Chinese study, which recommended the optimal cholesterol level centered at 170 mg/dl [4].

There are several plausible mechanisms that may underlie the protective effects of cholesterol on cognitive functions: first, a systemic hypolipidemic state may become a driving force behind cholesterol efflux in the brain, leading to depletion of myelin from its nerve building blocks. Second, cholesterol exhaustion causes neurodegenerative fragmentation and teardrop varicose enlargement of neurons [20]. Third, Ainiyet and Rybakowski have found a relationship between low TC and lower activity of central serotonergic release which affects the cognition, mood, and aggressive behavior. Fourth, hyperlipidemia has emerged in a recent analysis as protective against white matter hyperintensity burden accumulation [21].

High-density lipoprotein cholesterol and cognitive functions

A higher level of HD-CL is known to be protective against cardiovascular events and has also been associated with better cognitive performance in older adults.

Atzmon *et al*. [22] have found that plasma HDL-C levels correlated significantly with cognitive score.

In our study, we found that MMSE, MAS total memory score, verbal memory, and visual memory had a direct significant correlation with HDL-C.

This result was supported by a study carried out in Czech Republic in which it was found that HDL-C was associated with better cognitive scores [23].

The benefits of HDL-C may be attributed to first, its ability to prevent aggregation and polymerization of β-amyloid by maintaining its solubility in the cerebrospinal fluid and plasma, thus decelerating or even hindering the development of AD [20]; second, it reverses the LDL-induced impairment of endothelium-dependent relaxation by removing lysophosphatidylcholine and preventing it from acting on the endothelium [24].

On the contrary, HDL is blamed for cognitive decline as it is supposed to be associated with an increased number of neurofibrillary tangles and neuronal plaques [25]. But on the other side, there is the opinion that HDL-C is not associated with cognitive performance over time or the risk of mild cognitive impairment [26].

Low-density lipoprotein cholesterol and cognitive functions

LDL-C, the bad cholesterol, is always accused for increasing the risk of cardiovascular diseases. From a neurological point of view, there are many conflicts about the role of LDL-C and cognitive performance.

Ancelin *et al*. [27] found that there is no significant correlation between LDL-C and cognitive functions; the same result was confirmed by He *et al*. [28].

In our study, it was noticed that there was negative significant correlation between LDL-C and MMSE and MAS total score, indicating the deleterious effect of increasing LDL-C levels on cognitive functions.

These results, like Moroney and colleagues result, which was conducted on cognitively normal participants, found that a higher level of LDL-C was significantly associated with increased risk of cognitive impairment [29].

On the contrary, there is Sterling who found that higher plasma LDL-C levels were associated with better executive function and fine motor performance in old nondemented Parkinson patients [30]; the same result was supported by Zhou *et al*. [14].

LDL-C-associated bad cognitive function may be due to: first, LDL-C plays a role in forming plaque,

that is, atherosclerosis [3]; second, LDL-C inhibits endothelium-dependent arterial relaxation through its increased lysophosphatidylcholine; third, LDL-C leads to provocation of an inflammation response, promotion of coagulation, an increase in the activity of substances that cause vasoconstriction, and inhibition of others that cause vasodilatation [24].

Strengths and limitations

A strength of this study is all participants had no history of lipid-lowering drugs which may affect the accurate level of lipid profile components. Also, two batteries of cognitive testing were used MMSE and MAS, as MAS has more variables to test (short, verbal, and visual memory) which add to MMSE the accurate testing of cognitive functions.

Some limitations of this study must be mentioned. The main limitation of this study is that it lacks a follow-up record for our participants either with or without prescription of specific treatment either for memory impairment or dyslipidemia.

Other limitations are the small sample size and the cross-sectional study design, which does not allow for the detection of cause–effect relationships, but only of associations between the studied variables.

Conclusion

High serum TC levels, HDL-C, and low LDL-C may have protective effects on cognitive functions. However, we could not confirm if there is a dual correlation between serum TC and Hcy levels on cognitive functions, as all our participants had normal Hcy levels.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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