Therapeutic management of diseases based on fuzzy logic system- hypertriglyceridemia as a case study

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ABSTRACT

The support systems for assisting clinical decision highly improve the quality and efficiency of the therapeutic and diagnostic treatment in medicine. The proper implementation of such systems can emulate the reasoning of health care professionals in such a way that suggest reasonable decisions on patient treatment. The fuzzy logic system can be considered as one of the efficient techniques for converting a complex decision tree that usually facing the physician into artificial intelligent procedure embedded in a computer program. So many properties in fuzzy logic system that can facilitate the process of medical diagnosis and therapeutic management. In this paper, a system for therapeutic management of hypertriglyceridemia was efficiently realized using a fuzzy logic technique. The obtained results had shown that the proposed fuzzy logic contributes a reliable managing procedure for assisting the physicians and pharmacist in treating the hypertriglyceridemia. Many different hypertriglyceridemia treatment cases showed a perfect matching decision between the standard guidelines and that given by the proposed system.

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1. INTRODUCTION

The classical methods of medical diagnostic, which are mainly rely on physician and pharmacist memory, is hesitating decision and sometimes imprecision that may cause patient death. However, artificial intelligence continues to tempt engineers to make life easier and smart. These topics covers the ways that human being recognizes, classifies, and takes decisions. Therefore, one can find applications in industry [1]-[3] information security [4], [5], and medical engineering [6]-[8]. The availability of several computer algorithms and systems based on artificial intelligent can be utilized to assist the medical decision process in order to ensure accuracy and precision [9]-[11]. One of such system is fuzzy logic which are mostly based on the principles of using human language in describing thoughts, feelings and impressions [12].

Hypertriglyceridemia is one of the most common lipid abnormalities in clinical practice. It is appeared as a combination of multiple genetic variations with certain lifestyle and environmental factors. Common secondary causes include obesity, uncontrolled diabetes, alcohol misuse, and many commonly used medications. Treating these causes and enhancing lifestyle choices, including diet system, is important before starting drug therapy. The goal of drug therapy is to reduce the risk of cardiovascular disease in patients with moderate and severe hypertriglyceridemia [13]. The role of hypertriglyceridemia, as a risk factor of atherosclerotic cardiovascular disease, and best drug treatment, including optimal and emerging therapies are summarized in research terms as hypertriglyceridemia management. This includes optimal guidelines, statements, and systematic protocol that were reviewed by professional health care medical groups. In this work, the fuzzy logic is used to assist and address the uncertainty and imprecision that may occurred in traditional medical diagnostic practice. The system is tailored to be used within graphic use interface (GUI) in the therapeutic management of hypertriglyceridemia.

2. RELATED WORKS

The therapeutic management decisions taken by health care professionals rely on experience, scientific knowledge, familiarity and perception of the medical scientist. As the complexity of medical disease increases, it becomes difficult to follow a particular path of treatment without medication error. Therefore, the fuzzy logic can be considered as a powerful reasoning technique that can handle uncertainties and imprecision. A medical therapeutic management system based on fuzzy model involve an integration of physician and pharmacist medical information and guideline treatment for diseases therapies. These consensus statements, guidelines and systematic reviews for the last two decades were presented in [13]. However, therapeutic management and medical diagnosis systems based on fuzzy logic were published recently for many diseases such as chronic kidney disease, heart disease, renal cancer, prostate cancer and others. Following are some selected papers in this field.

Jahantigh [14] developed a fuzzy logic system which can be used for kidney disease diagnosis. The approach based on utilizing the knowledge of professional physicians and save it in tables as disease profiles. The study shows the results of the kidney disease diagnosis (e.g., kidney stone) via fuzzy logic were compatible to some extent with those of kidney physicians.

Singla *et al.* [15] developed and designed a fuzzy expert system to recognize the current situation of chronic kidney disease. The proposed fuzzy rule-based expert system is developed with the aid of clinical practice guidelines, database, and the knowledge of medical professional team. It makes use of input variables like nephron functionality, blood sugar, diastolic blood pressure, systolic blood pressure, age, body mass index (BMI), and smoke. the detection of chronic kidney disease is a serious clinical problem that comprises imprecision, and the use of fuzzy inference system is suggested to overcome this issue. The authors concluded that the proposed system could support doctors and assist them in their medical decisions without replacing their notable work.

Naseer *et al.* [16] proposed diagnosis heart disease using Mamdani fuzzy inference (DHD-MFI) based expert system which intelligently diagnoses heart disease. They used age, chest pain, ECG, blood pressure systolic, diabetic and cholesterol as a fuzzy system input while the output is the supporting clinical heart disease decision. The proposed DHD-MFI based expert system gives 94% overall accuracy.

Alam *et al.* [17] demonstrated an integrated view of deploying smart disease diagnosis using the Internet of Things (IoT) empowered by the fuzzy inference system (FIS) as a classifier to diagnose various diseases. The system can track symptoms firmly to diagnose diseases through IoT and FIS smartly and efficiently. Different coefficients have been employed to predict and compute the characterized disease's severity for each sign of disease. However, acquiring the required data is a big challenge to improve the performance of such system.

Adnan *et al.* [18] applied the predictive model in detecting chronic kidney disease (CKD) using fuzzy logic technique. Their fuzzy detecting system's input data were blood urea nitrogen test, estimated glomerular filtration test and serum creatinine test. The output is the likelihood of CKD as (yes or no). In their study, 70 patients' clinical tests were used as a set of data. The result shows that 47 out of 70 patients were detected as CKD patients. As a conclusion, early detection of CKD is very important to treat the disease at an early stage. This will allow patients to take an early action and follow up treatments or consultations with nephrologist to avoid any serious complications.

Jindal *et al.* [19] used fuzzy and adaptive neuro-fuzzy inference systems as intelligent medical diagnostic systems to diagnose renal cancer. They utilized two layers in their fuzzy inference system. The first layer indicates the existing of renal cancer (yes or no), while the second layer characterized the current stage of the disease. The comparison between the performance of developed systems has been done by taking some suitable parameters such as classification accuracy, sensitivity, specificity and precision. The results obtained from this comparison study showed that the intelligent medical system developed by using a neuro-fuzzy model gives the more precise and accurate results than fuzzy system.

Improta *et al.* [20] proposed fuzzy logic based clinical decision support system (CDSS) for the evaluation of renal function in post-transplant patients. Two parameters were chosen for this purpose, mainly the proteinuria and the glomerular filtration rate. The systems show an accuracy of more than 90% and the outputs are provided smart read graphics, so that physicians can intuitively monitor the patient's clinical status, aiming to improve drugs dosage and minimize medication errors.

Rusliyawati *et al.* [21] compared the accuracy of the fuzzy model with the predicted status given by prostate cancer specialists. Prediction is made based on prostate specific antigen data, age, and patient prostate volume which represent the independent variables. The dependent variable is the risk of prostate cancer as low, moderate, high and very high-level output.

3. RESEARCH METHOD

The aim of the research is to reach a similar decision between the proposed fuzzy logic system and the physician's decision to be helpful in following up on the patient's condition. This section consists of two parts: the first part includes guidelines for managing hyperlipidemia as seen by the physicians and/or the pharmacist's point of view as described in the section 3.1. The second part demonstrates the functioning of the proposed fuzzy logic system to replace the above management guidelines in the context of the AI concept which is explained in section 3.2 fuzzy logic management system (FLTM) for hypertriglyceridemia.

3.1. The hypertriglyceridemia management guideline

High triglyceride levels in blood contribute, with other factors, to cardiovascular mortality in different countries. Single elevation of serum triglyceride level may be the result of:
1) Lipid metabolism disorder.
2) Due to the use of medicines such as estrogens, retinoid, corticosteroids, some immunosuppressant.
3) A component of the metabolic syndrome or type 2 diabetes mellitus.

However, many individuals have a mixed dyslipidemia that include elevated triglyceride levels and abnormal levels of other lipoproteins. Lipid lowering therapies play an important role in the prevention of cardiovascular diseases. The principle for management of hypertriglyceridemia divided into two parts, the non-pharmacological and the pharmacological managements. This is according to the serum triglyceride level (TG) and the presence of other risk factors [22]. Three main drugs are used for treating dyslipidemia:
1) Statins: these reduce cholesterol synthesis by inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase (HMG-CoA reductase) enzyme resulting in reduction of low-density lipoprotein cholesterol (LDL-C) by up to 60%, reduction of triglyceride (TG) by up to 40% and increasing of high-density lipoprotein cholesterol (HDL-C) by up to 10%.
2) Fibrate: control the synthesis and catabolism of triglycerides by stimulate the peroxisome proliferator-activated receptor (PPAR). TG reduced by up to 50% and HDL-C increased by up to 20%.
3) Fish oil (omega 3): these are potent inhibitor of TG and LDL-C formation. Taking omega 3 on daily basis can result in up to 50% reduction in TG levels [23].

If the first serum triglyceride level (TG_1) between 150 and 200 mg/dL, in this case, no pharmacological intervention required, (see Figure 1) [24]. Diet, exercise and lifestyle optimization are the primary modes of treatment. Pharmacological treatments are recommended when serum triglyceride level elevated to more than 200 mg/dL. According to the treatment regimen of hypertriglyceridemia shown in Figure 1 and for the case of mild and moderate elevation of TG levels (i.e., 200 to 350 mg/dL), single therapy (statin of fibrate alone) are sufficient to randomize the case and return the TG to its normal levels. However, in sever elevation (i.e., 450 mg/dL and above) combinations of double or triple therapy are recommended to control the case, according to TG_2 or TG_3.

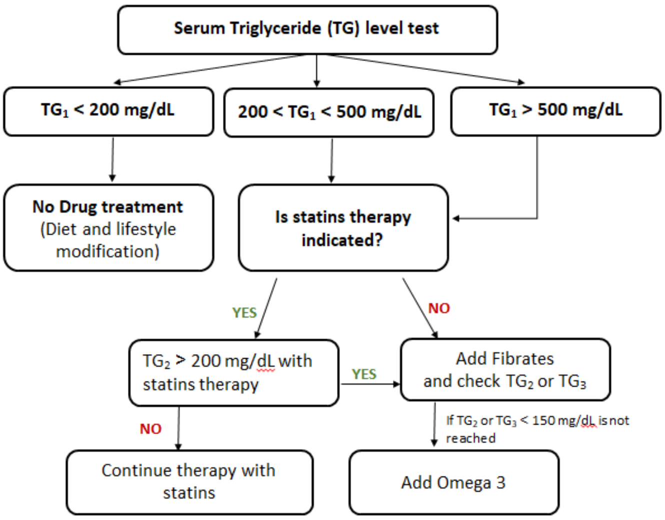


Figure 1. Treatment regimen of hypertriglyceridemia [24]

3.2. The fuzzy logic treatment management (FLTM) system for hypertriglyceridemia

The aim of the FLTM system is to assist the physician and pharmacist to follow the treatment regimen of hypertriglyceridemia as shown in Figure 1 within smart support medical decision based on artificial intelligent techniques. Since the medical decision is based on many quantitative tests, it is proposed in this work to build a fuzzy logic system that can give the same treatment regimen of hypertriglyceridemia. The FLTM system consists of three parts as shown in Figure 2.

1) The smart GUI inputs which support the data of statins drug and fibrates drug that taken by the patient (yes = 1 and no = 0) as well as the numerical values of his TG's tests.
2) The fuzzy logic system that gives a medical decision in the range between zero and one.
3) The smart GUI output which translates the FL system output into understandable text for the physician and/or the pharmacist.

However, this paper will concentrate on the second part only as it represents the heart of the proposed FLTM system for hypertriglyceridemia. The FL system is implemented under MATLAB environment [25]. As mentioned earlier, the inputs to the proposed FL system is supported by the smart GUI inputs. These inputs mainly are:

1) Statins drug and/or fibrates drug (value of "1" for having drug and value of "0" for not).
2) Triglyceride chemical test (TG) performed on request each time.

Accordingly, the treatment regimen of hypertriglyceridemia can be performed using FL in four phases (see Figure 3):

a) Phase 1 in which the patient did not take either the statins or fibrates drugs and he/she have done the TG test for the first time (i.e TG_1)
b) Phase 2 in which the patient has taken the statins drug but not the fibrates drug. Also, he/she have done the TG test for the second time (i.e having the numerical values of TG_1 and TG_2).
c) Phase 3 in which the patient has taken the statins drug and the fibrates drug. Also, he/she have done the TG test for the third time (i.e having the numerical values of TG_1, TG_2 and TG_3).
d) Phase 4 in which the patient did not take the statins drug while the fibrates drug has been taken. Also, he/she have done the TG test for the second time (i.e having the numerical values of TG_1 and TG_2).

Each of these phases has its own FL system with proper input membership functions that represent its inputs and proper output membership functions.

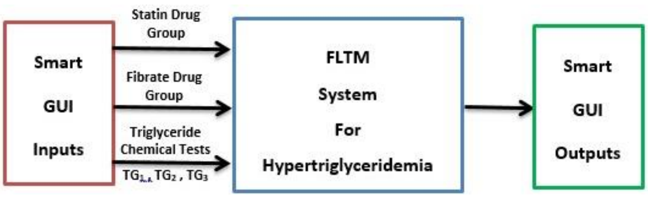


Figure 2. FLTM system input/output for hypertriglyceridemia

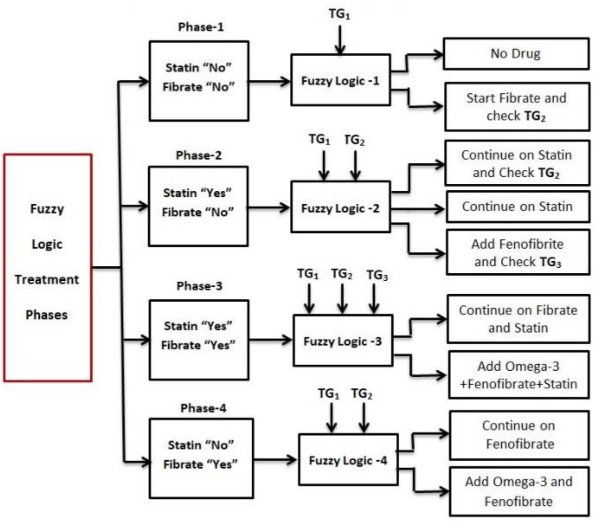


Figure 3. The proposed FLTM system for hypertriglyceridemia

4. RESULTS AND DISCUSSION

According to the patient's data from the smart GUI input, the corresponding phase will be activated. For phase 1, ten cases (or patients) are considered in this phase in which the statins drug = 0 and the fibrates drug = 0. The numerical values of their TG_1 test are shown in Table 1. The TG_1 membership function and the output membership function are shown in Figure 4(a) and Figure 4(b). The FL values for $TG_1 = 190$ and $TG_1 = 210$ are shown in Figure 4(c) and Figure 4(d). The rules that governed the input/output variables:

1) If (TG_1 is v.good) then (decision is no.drug) (1)
2) If (TG_1 is bad) then (decision is str.fbrat) (1)
3) If (TG_1 is v.bad) then (decision is str.fbrat) (1)

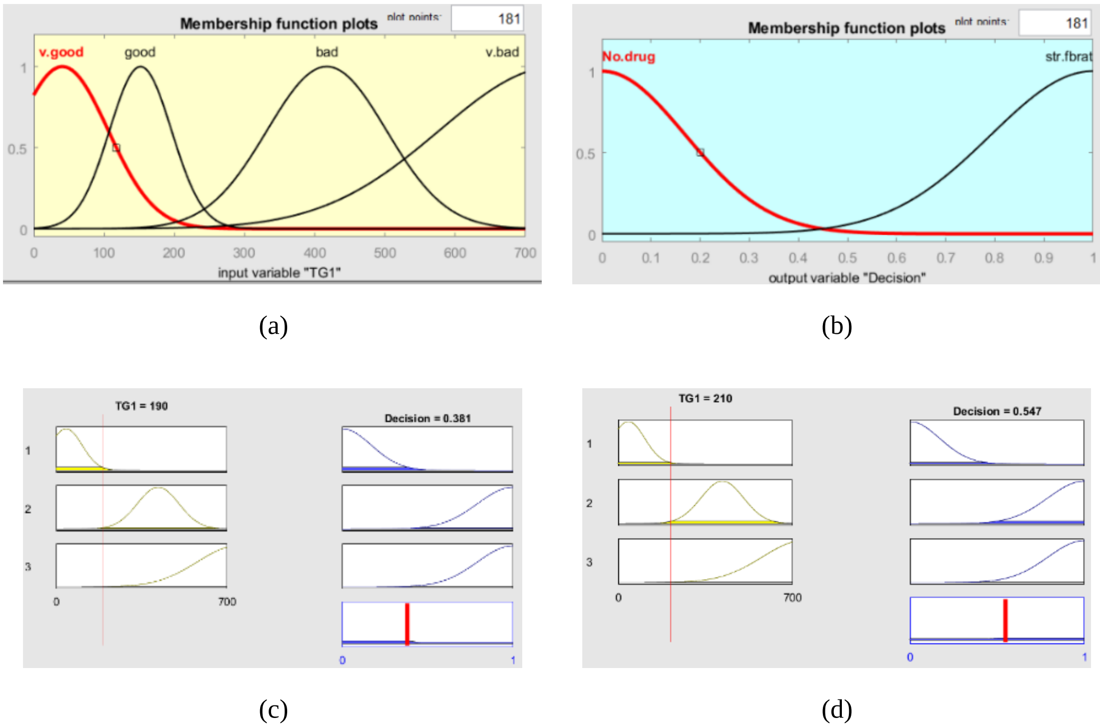


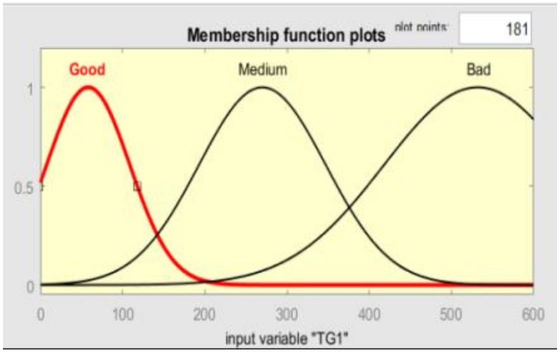
Figure 4. The fuzzy logic system of phase 1: (a) the membership function of TG_1; (b) the membership function of FL output; (c) the FL output at $TG_1 = 190$; and (d) the FL output at $TG_1 = 210$

Table 1. The result of phase (1) "without statins and without fibrates"

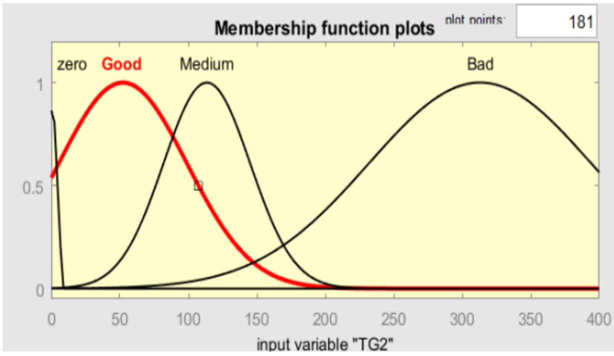
Level	Case no.	TG_1 value mg/dL	Fuzzy output	Medical decision
Normal level	1	100	0.149	No drug
	2	120	0.165	No drug
	3	165	0.246	No drug
Borderline level	4	190	0.381	No drug
	5	200	0.463	No drug
	6	210	0.547	Start fibrates and check TG_2
High level	7	225	0.65	Start fibrates and check TG_2
	8	280	0.773	Start fibrates and check TG_2
	9	320	0.806	Start fibrates and check TG_2
	10	400	0.836	Start fibrates and check TG_2
The smart GUI output translation of the FL output.			Normal level of TG is <= 200	
			Fuzzy output from 0 to 0.5 == "No drug"	
			Fuzzy output from 0 to 0.5 == "Start fibrates and check TG_2"	

For phase 2, twelve cases (or patients) are considered in this phase in which the statins drug = 1 and the fibrates drug = 0. The numerical values of their TG_1 and TG_2 tests are shown in Table 2. The TG_1 and TG_2 membership functions and the output membership function are shown in Figure 5(a), Figure 5(b), and Figure 5(c), respectively. The FL values for ($TG_1 = 350$, $TG_2 = 0$), ($TG_1 = 405$, $TG_2 = 148$), and ($TG_1 = 436$, $TG_2 = 298$) are shown in Figure 5(d), Figure 5(e), and Figure 5(f), respectively. The rules that governed the input/output variables:

1) If (TG_1 is bad) then (decision is cont. on statin + check TG_2) (1)
2) If (TG_1 is v.bad) and (TG_2 is v good) then (decision is cont. statin) (1)
3) If (TG_1 is v.bad) then (decision is cont. on statin + check TG_2) (1)
4) If (TG_1 is v.bad) and (TG_2 is good) then (decision is cont. statin) (1)
5) If (TG_1 is bad) and (TG_2 is good) then (decision is cont. statin) (1)
6) If (TG_1 is bad) and (TG_2 is v good) then (decision is cont. statin) (1)
7) If (TG_1 is bad) and (TG_2 is bad) then (decision is add.fbrat + check TG_3) (1)
8) If (TG_1 is v.bad) and (TG_2 is v.bad) then (decision is add.fbrat + check TG_3)
9) If (TG_1 is v.bad) and (TG_2 is bad) then (decision is add.fbrat + check TG_3) (1)



(a)



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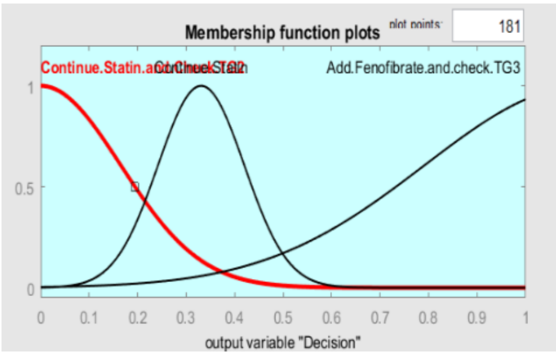

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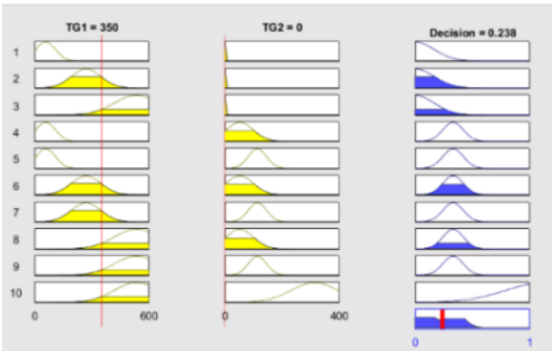

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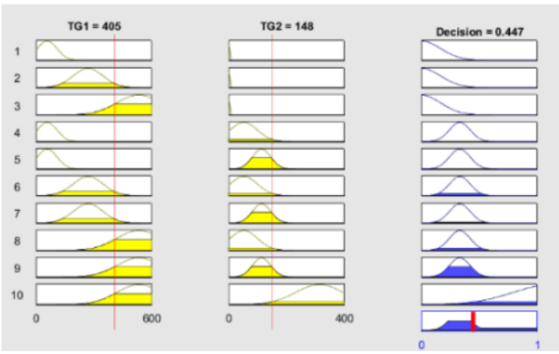

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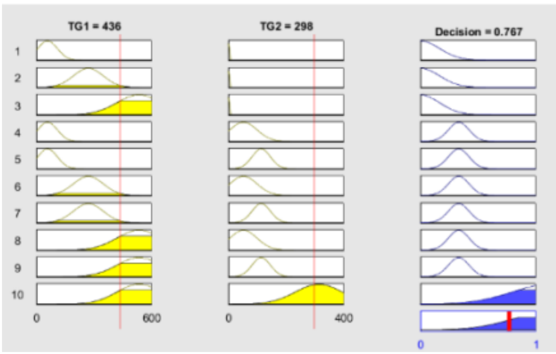


(f)

Figure 5. The fuzzy logic system of phase 2: (a) the membership function of TG_1; (b) the membership function of TG_2; (c) the membership function of FL output; (d) the FL output at [TG_1 = 350, TG_2 = 0]; (e) the FL output at [TG_1 = 405, TG_2 = 148]; and (f) the FL output at [TG_1 = 436, TG_2 = 298]

Table 2. The result of phase (2) “with statins and without fibrates”

Case no.	TG_1 value	TG_2 value	Fuzzy output	Medical decision
1	227	none	0.217	Continue on statins and check TG_2
2	269	none	0.216	Continue on statins and check TG_2
3	350	none	0.238	Continue on statins and check TG_2
4	438	none	0.226	Continue on statins and check TG_2
5	225	119	0.368	Continue on statins
6	273	140	0.475	Continue on statins
7	315	138	0.496	Continue on statins
8	405	148	0.447	Continue on statins
9	235	173	0.259	Add fibrates and check TG_3
10	255	160	0.513	Add fibrates and check TG_3
11	351	211	0.702	Add fibrates and check TG_3
12	436	298	0.767	Add fibrates and check TG_3
The smart GUI output translation of the FL output.		TG_1 rang (200–700) TG_2 rang (100–500) 0 – 0.29 “continue on statins and check TG_2” 0.3 – 0.55 “continue statins” 0.55 – 1 “add fibrates and check TG_3”		

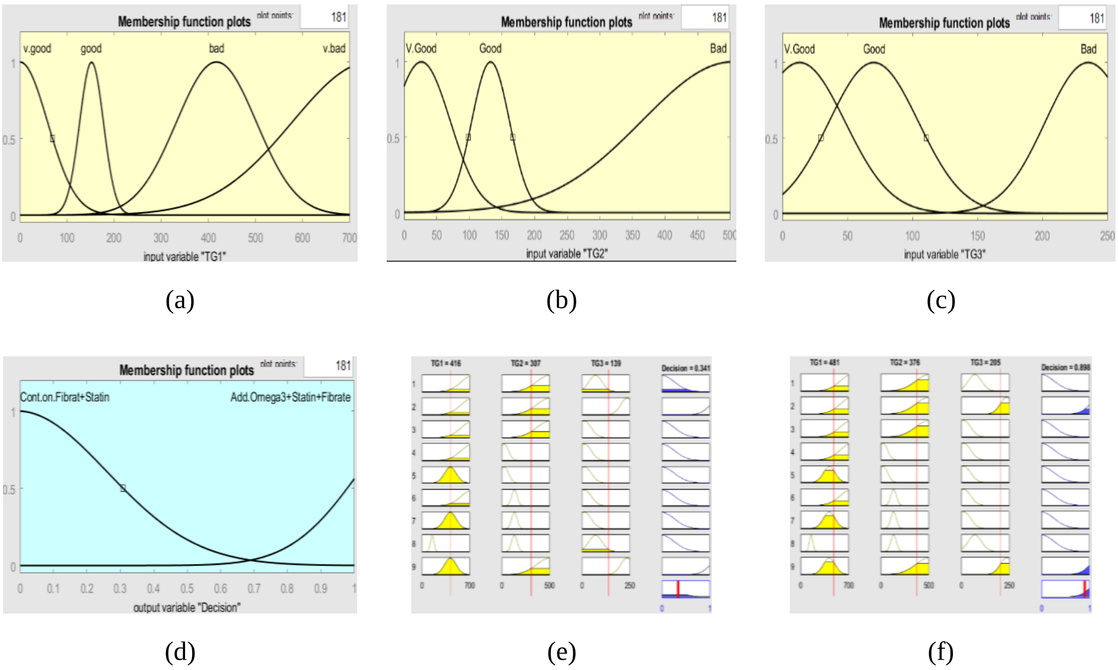


Figure 6. The fuzzy logic system of phase 3: (a) the membership function of TG_1; (b) the membership function of TG_2; (c) the membership function of TG_3; (d) the membership function of FL output; (e) the FL output at [$TG_1 = 416$, $TG_2 = 307$, $TG_3 = 139$]; and (f) the FL output at [$TG_1 = 481$, $TG_2 = 376$, $TG_3 = 205$]

For phase 3, ten cases (or patients) are considered in this phase in which the statins drug = 1 and the fibrates drug = 1. The numerical values of their TG_1, TG_2, and TG_3 tests are shown in Table 3. The TG_1, TG_2, and TG_3 membership functions and the output membership function are shown in Figures 6(a), Figure 6(b), Figure 6(c) and Figure 6(d), respectively. The FL values for ($TG_1 = 416$, $TG_2 = 307$, $TG_3 = 139$) and ($TG_1 = 481$, $TG_2 = 376$, $TG_3 = 205$) are shown in Figure 6(e) and Figure 6(f), respectively. The rules that governed the input/output variable:

1) If (TG_1 is v.bad) and (TG_2 is bad) and (TG_3 is good) then (decision is cont. on fibrat + statin) (1)
2) If (TG_1 is v.bad) and (TG_2 is bad) and (TG_3 is bad) then (decision is add omega3 + statin + fibrate) (1)
3) If (TG_1 is v.bad) and (TG_2 is bad) and (TG_3 is v.good) then (decision is cont. on fibrat + statin) (1)
4) If (TG_1 is v.bad) and (TG_2 is v.good) and (TG_3 is v.good) then (decision is cont. on fibrat + statin) (1)
5) If (TG_1 is bad) and (TG_2 is v.good) and (TG_3 is v.good) then (decision is cont. on fibrat + statin) (1)
6) If (TG_1 is v.bad) and (TG_2 is good) and (TG_3 is v.good) then (decision is cont. on fibrat + statin) (1)
7) If (TG_1 is bad) and (TG_2 is good) and (TG_3 is v.good) then (decision is cont. on fibrat + statin) (1)
8) If (TG_1 is good) and (TG_2 is good) and (TG_3 is good) then (decision is cont. on fibrat + statin) (1)
9) If (TG_1 is bad) and (TG_2 is bad) and (TG_3 is bad) then (decision is add omega3 + statin + fibrate) (1)

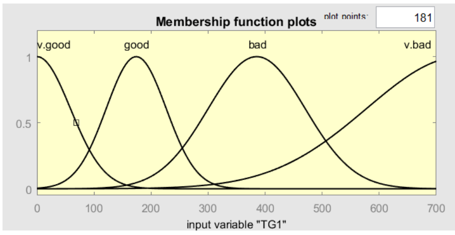
For phase 4, ten cases (or patients) are considered in this phase in which the statins drug = 0 and the fibrates drug = 1. The numerical values of their TG_1 and TG_2 tests are shown in Table 4. The TG_1 and TG_2 membership functions and the output membership function are shown in Figure 7(a), Figure 7(b) and Figure 7(c), respectively. The FL values for (TG_1 = 343, TG_2 = 137) and (TG_1 = 353, TG_2 = 269) are shown in Figure 7(d) and Figure 7(e), respectively. The rules that governed the input/output variables:

1) If (TG1 is bad) and (TG2 is good) then (decision is cont. on fibrate) (1)
2) If (TG1 is bad) and (TG2 is bad) then (decision is add omega3 + fibrate) (1)

Table 3. The result of phase (3) “with statins and with fibrates”

Case no.	TG_1 value	TG_2 value	TG_3 value	Fuzzy output	Medical decision
1	357	208	133	0.372	Continue on fibrates and statin
2	377	223	141	0.373	Continue on fibrates and statin
3	416	307	139	0.341	Continue on fibrates and statin
4	453	337	145	0.383	Continue on fibrates and statin
5	447	351	149	0.424	Continue on fibrates and statin
6	361	217	167	0.715	Add omega3 + fibrates + statins
7	388	227	171	0.761	Add omega3 + fibrates + statins
8	423	314	183	0.86	Add omega3 + fibrates + statins
9	446	357	155	0.51	Add omega3 + fibrates + statins
10	481	376	205	0.898	Add omega3 + fibrates + statins

The smart GUI output translation of the FL output.
TG_1 rang (200 – 700)
TG_2 rang (100 – 500)
TG_3 rang (150 – 500)
0 – 0.5 “continue on fibrates and statins”
0.5 – 1 “add omega3 + fibrates + statins”



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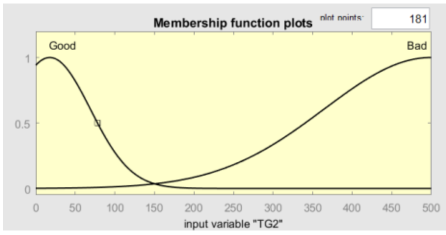

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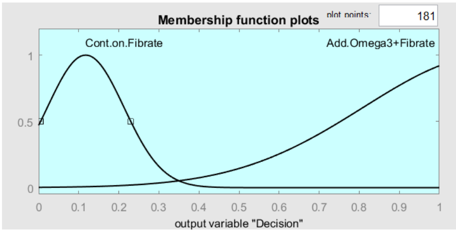

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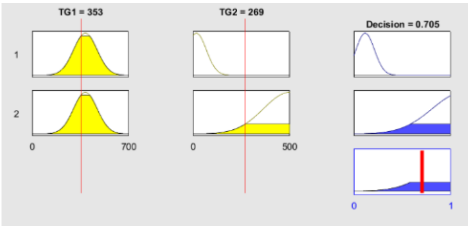

(e)

Figure 7. The fuzzy logic system of phase 4: (a) the membership function of TG_1; (b) the membership function of TG_2; (c) the membership function of FL output; (d) the FL output at [TG_1 = 343, TG_2 = 137]; and (e) the FL output at [TG_1 = 353, TG_2 = 269]

Table 4. The result of phase (4) “without statins and with fibrates”

Case no.	TG_1 value	TG_2 value	Fuzzy output	Medical decision
1	256	123	0.292	Continue on fibrates
2	343	137	0.389	Continue on fibrates
3	387	144	0.447	Continue on fibrates
4	293	148	0.481	Continue on fibrates
5	233	114	0.247	Continue on fibrates
6	263	164	0.578	Add omega3 and fibrates
7	291	172	0.603	Add omega3 and fibrates
8	324	189	0.632	Add omega3 and fibrates
9	214	155	0.532	Add omega3 and fibrates
10	353	269	0.705	Add omega3 and fibrates
The smart GUI output translation of the FL output.		TG_1 rang (200 – 500) TG_2 rang (100 – 500) 0 – 0.5 “continue on fibrates” 0.5 – 1 “add omega3 and fibrates”		

5. CONCLUSION

In this research, the decision tree of the hypertriglyceridemia management guideline has been transformed into a smart artificial intelligent program using fuzzy logic technique. By taking many cases, a perfect agreement is obtained when matching medical decision taken by the physician and/or pharmacist with that obtained by the FL system. Moreover, the accuracy of medical decision can be altered by manipulating the FL rules and membership functions if any deep scientific research will be considered in future on some cases as recommended by the physicians. This program can be extended to cover many treatment management guidelines and put it in package as a support system for assisting clinical decision. Also, this package will be useful for training and examining students in medicine and pharmacy colleges.

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