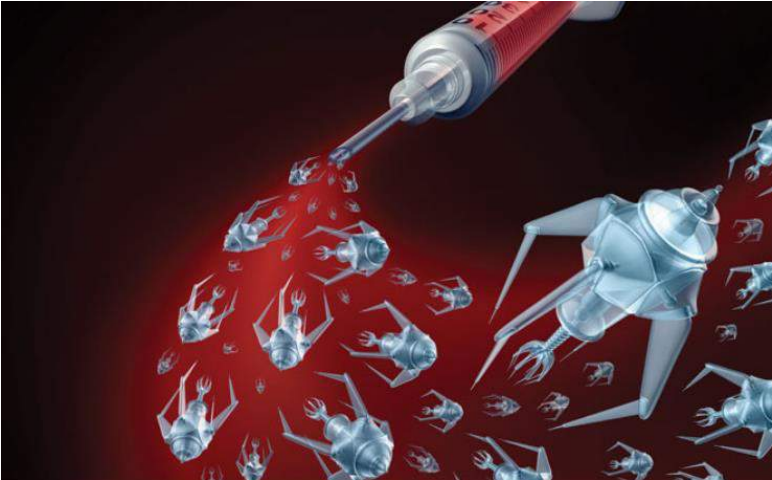


Teknolojide Gelecek Beklentileri (Yapay Zeka ve Nano Teknoloji)

Prof. Dr. Mustafa Cesur

Ankara Güven Hastanesi



Accurate and reproducible readings from different sites of the body

HIRF:

- From finger: 95, 93, 94
- From palm: 97
- From wrist: 94
- From belly: 95
- From Eye: 96
- Urine: 95, 93, 99
- Saliva: 95

Strip:

Accu-check: 96

D-Smart: 91



VIDEO-2021-03-23-14-02-30 (1).MOV





Glucose Testing Comparison sheet 29-10-2019

	HRRF			Peripheral Blood Test			Reference Lab ACCU CHECK	Standard Accu Check	average HRRF	Average Lab	Average Strip	Accuracy (HRRF/ LAB)	Accuracy (Strip/ LAB)	Accuracy (HRRF/ Strip)
	Reading 1	Reading 2	Reading 3	SCA Labs	Mediabs	Alkhalid Hospital								
				Mindray	Roche	Roche								
Volunteer 1	94	95	93	95	94	98	111	127	94	96	109	98.9%	124.4%	79.0%
Volunteer 2	310	327	300	313	306	318	298	276	312	312	287	100.0%	91.9%	108.8%
Volunteer 3	455	490	426	461	509	532	432	470	424	501	453	94.6%	90.1%	105.0%
Volunteer 4	110	x	104	92	91	94	83	94	107	92	89	115.9%	95.8%	120.9%
Volunteer 5	175	189	151	185	182	192	168	180	172	186	174	92.1%	93.4%	98.7%
Volunteer 6	281	273	277	256	258	258	228	252	277	257	240	107.6%	93.3%	115.4%
Volunteer 7	100	104	85	86	86	92	88	90	96	88	89	109.5%	101.1%	108.2%
Volunteer 8	191	182	192	267	257	271	240	264	188	255	252	71.1%	95.1%	74.7%
Volunteer 9	89	100	87	85	84	89	75	85	93	86	80	108.1%	91.0%	116.3%
Volunteer 10	92	92	90	83	83	85	94	98	91	84	98	109.2%	114.7%	95.1%
Volunteer 11	200	234	243	216	213	222	220	224	229	217	223	105.4%	102.5%	102.8%
Volunteer 12	96	84	93	112	108	114	102	108	91	111	104	81.7%	94.8%	86.3%
Volunteer 13	168	160	166	167	168	167	169	163	97	163	160	93.5%	98.7%	94.8%
Volunteer 14	109	105	101	107	107	108	139	124	105	107	132	92.8%	122.5%	79.8%
Volunteer 15	100	108	99	96	96	98	94	99	102	97	97	105.9%	99.8%	106.0%
Volunteer 16	103	104	99	97	x	101	102	100	102	99	103	103.0%	103.5%	99.5%
Volunteer 17	91	85	92	89	88	93	94	91	89	90	93	99.1%	102.8%	96.6%
Volunteer 18	92	89	85	98	101	101	105	106	89	100	111	88.7%	110.5%	80.2%
Volunteer 19	91	86	105	95	96	101	112	120	95	97	124	97.6%	126.9%	76.9%
Volunteer 20	108	92	95	86	89	89	87	89	99	88	88	112.3%	100.0%	112.1%
Average:												99.6%	102.7%	97.9%

NANOTEKNOLOJİ

- Nanoteknoloji, hastalıkları doğru ve zamanında teşhis etmek için algılama teknolojileri ve minyatür cihazlar sunan önde gelen bir bilimsel tekniktir.
- Nanoteknolojinin ilaç dağıtımı alanında geniş bir uygulama yelpazesi vardır
- Ayrıca proteinlerin ve peptitlerin oral absorpsiyonunu basitleştirmek için nano taşıyıcılar spesifik ligandlarla modifiye edilir

Nanoteknoloji ile İlgili Bileşenlerin Boyut Alanları

- Nanoteknoloji ile 1 ile 100 nm arasında değişen gelişmiş özelliklere sahip malzemelerin üretilmesi mümkün hale gelmiştir.
- İlaç taşıyan nanoyapılar, virüslerle aynı boyuttadır (10 nm)
- Karbon ve polimer temelli yapılar büyük önem taşır

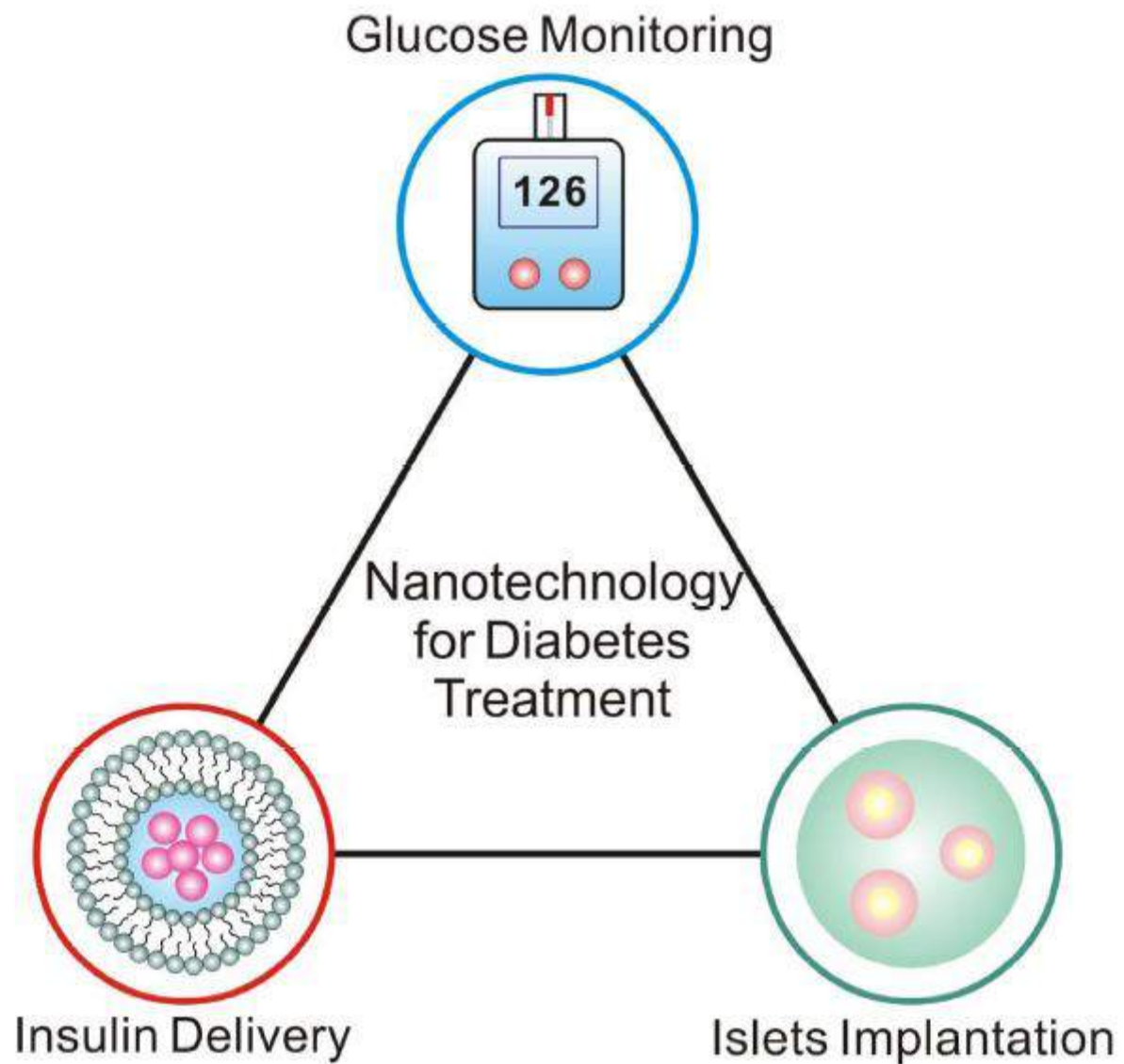
Nanopartiküllerin Avantajları

- Parenteral, oral, nazal, oküler, inhaler yolla uygulanabilir
- Yüzeye spesifik ligand ekleyerek, ilaçları spesifik hedef hücrelere yönlendirme
- Stabilite ve terapötik indeksi iyileştirir
- Toksik etkileri azaltır

Diyabet Tedavisinde Nanoteknoloji

- Biyolojik olarak uyumlu (biocompatible)
- Biyolojik olarak parçalanabilir (biodegradable)
- Etkili ve kullanımı güvenli
- Çeşitli ilaç dağıtım sistemlerinin tasarlanması
- Geliştirilmesi

için önemli bir platform



DİYABETTE NANOTEKNOLOJİYE YAKLAŞIM

TANI

1. Mikrofizyometer
2. İmpalante Edilebilen Sensor (Smart Tattoo)
3. Görüntüleme Yöntemleri

TEDAVİ

1. Nanopompalar
2. Nonotüpler
3. Uzun Süreli Sensor Sistemleri
4. "Smart Tattoo"lar
5. Kaplı İnsülin Nano Partikülleri
6. İnsülin Dışı Antidiyabetikler

Glukoz Sensörleri + Mikrofizyometer

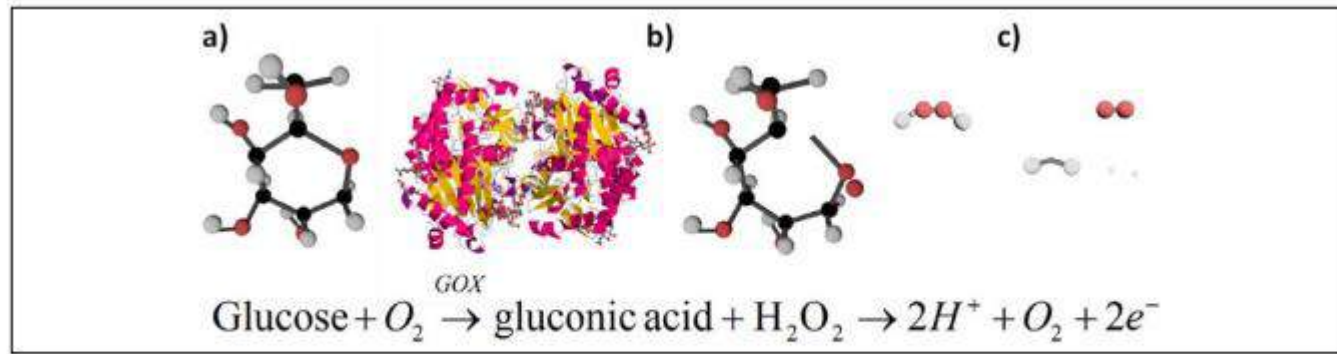


Figure 1. Basic working principle for glucose biosensors (molecules are not drawn to scale). (a) Glucose binds in the enzymatic binding pocket of glucose oxidase (GOX). (b) An applied potential catalyzes the oxidation of glucose to gluconic acid and hydrogen peroxide. (c) Hydrogen peroxide dissociates to O_2 , 2H^+ , and 2 free electrons; electrons are measured using electrochemical or optical techniques.

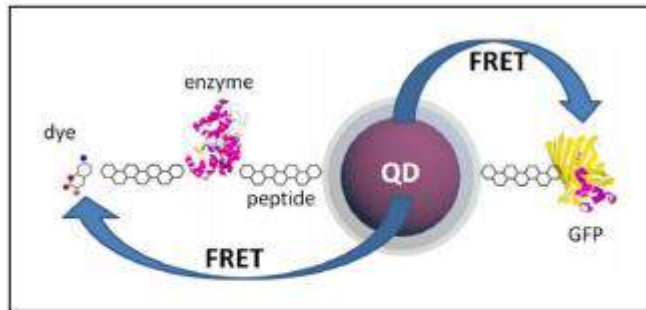


Figure 2. Conceptual schematic of a Förster resonance energy transfer (FRET) interaction between quantum dots (QD) and enzyme-dye conjugates (left) as well as QD-green fluorescent protein FRET pairing.

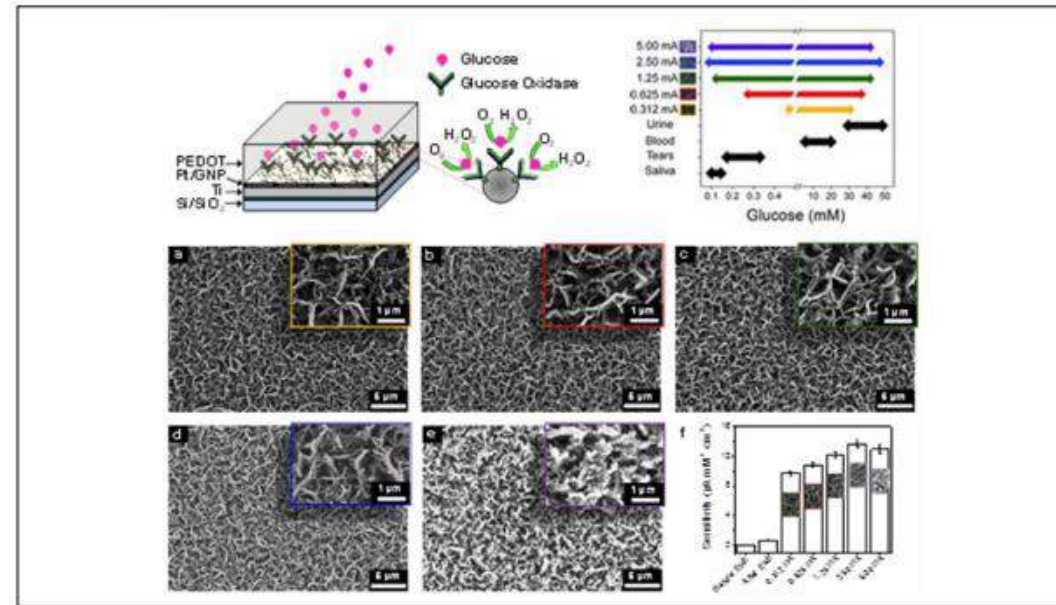


Figure 3. (Top Left) Tilted cross-sectional schematic illustrating the GOx/PEDOT biofunctionalized PtNP-MGPN glucose biosensor with adjacent magnified view portrayal of GOx immobilized on a single PtNP. Glucose binds within the GOx enzymatic pocket producing H_2O_2 while consuming O_2 . (a-e) Field emission scanning electron microscopy (FESEM) micrographs of PtNPs electrodeposited on MGPNs. Current pulses (500 ms) of (a) 312 μA , (b) 625 μA , (c) 1.25 mA, (d) 2.5 mA, and (e) 5.0 mA were used to electrodeposit Pt nanoparticles of distinct size and density onto the MGPNs. (f) Bar graph displaying the H_2O_2 sensitivity of the MGPN electrode (before and after the oxygen plasma etch) and the PtNP-MGPN electrodes. Errors bars show standard deviation for 3 different experiments. (Top Right). Glucose sensing ranges of the Pt-MGPN glucose biosensors (Pt electrodeposition current pulses of 312 μA , 625 μA , 1.25 mA, 2.5 mA, and 5.0 mA) as compared to glucose levels found in urine, blood, tears, and saliva. Reprinted with permission from *Advanced Functional Materials*.⁶⁸ Copyright 2012 Wiley-VCH.

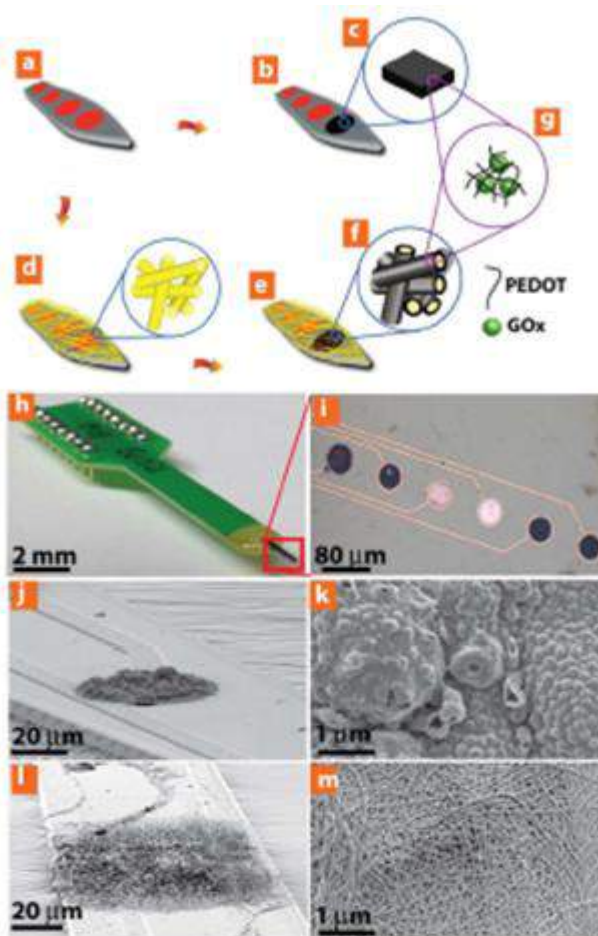
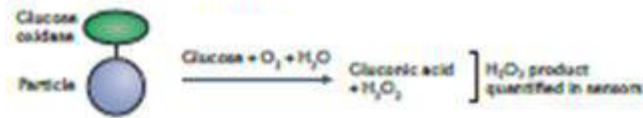


Figure 2.

Yang, et al investigated how nanowires can affect the sensitivity of amperometric glucose sensors. In this experiment, two types of sensors were developed; the first was formed by immobilizing GOx within a bulk hydrogel, and the second was formed by immobilizing GOx on the surface of conductive nanowires. This figure depicts a schematic of the two types of glucose concentration sensors: (a–c) A bulk hydrogel glucose sensor with embedded GOx. (a,d–g) A nanowire glucose sensor with embedded GOx. (h,i) The glucose sensor apparatus. (j–k) The bulk hydrogel-GOx sensing system. (l–m) The nanowire-GOx based glucose sensing system. The nanowire based sensor was more sensitive than the bulk film sensor, which was attributed to its larger surface area, increased GOx loading capacity, and lower electrical resistance. (Copyright 2014 John Wiley & Sons)

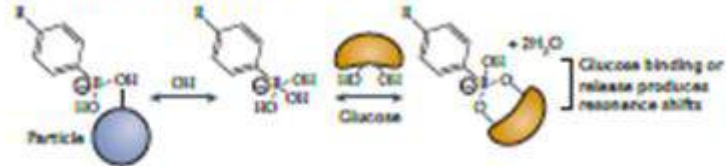
a Glucose-detecting molecules

Glucose oxidase-based sensors



- High glucose specificity
- Slow response rates
- Susceptible to pH and oxygen fluctuations

Sensors based on boronic acid derivatives



- Rapid response rates
- Long-term high fidelity
- Lack of glucose specificity

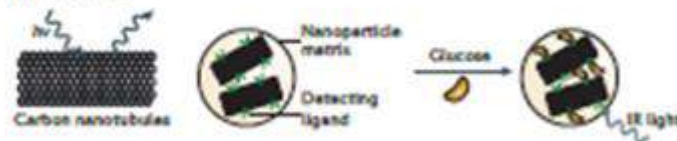
Sensors based on ConA or glucose-binding protein



- High glucose specificity
- Rapid response rates
- Susceptible to degradation

b Nanoparticles as transducers

Fluorescence



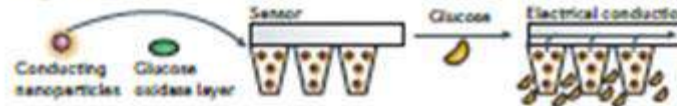
- Ultra-fast readout
- Long-term function without battery
- Improved precision in hypoglycaemic range

Indirect ratiometric



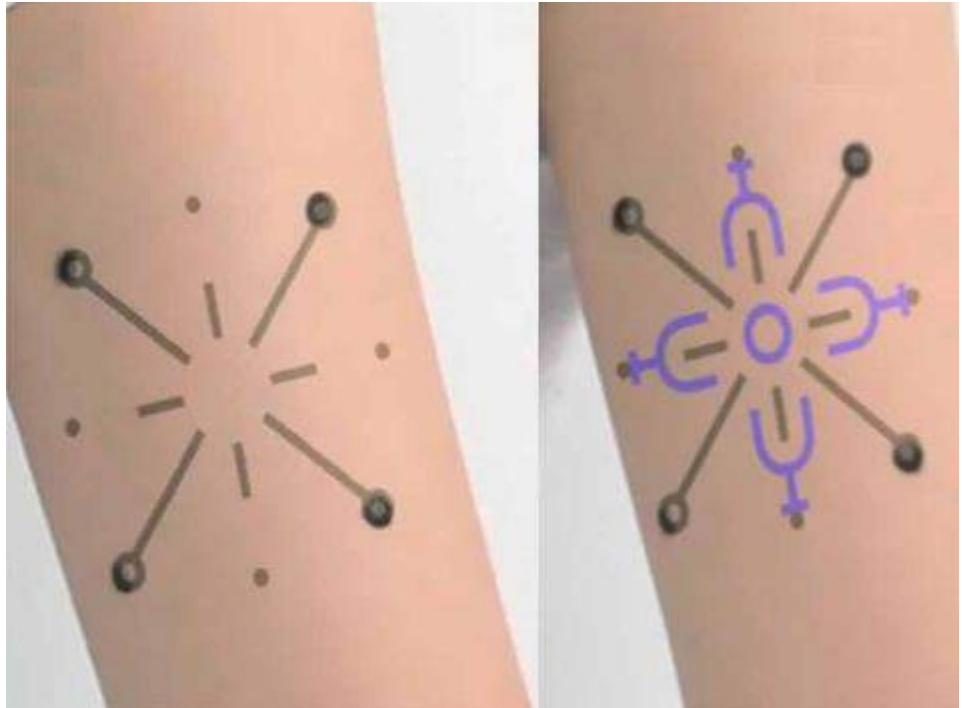
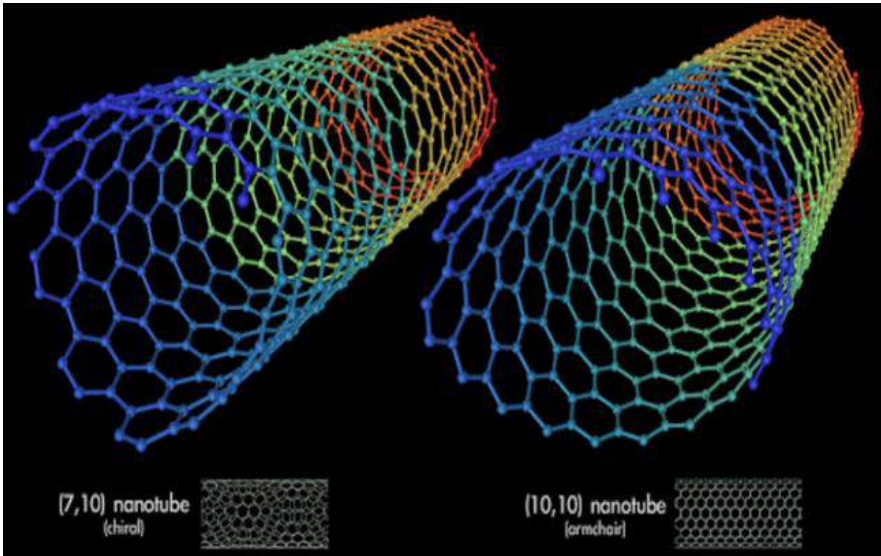
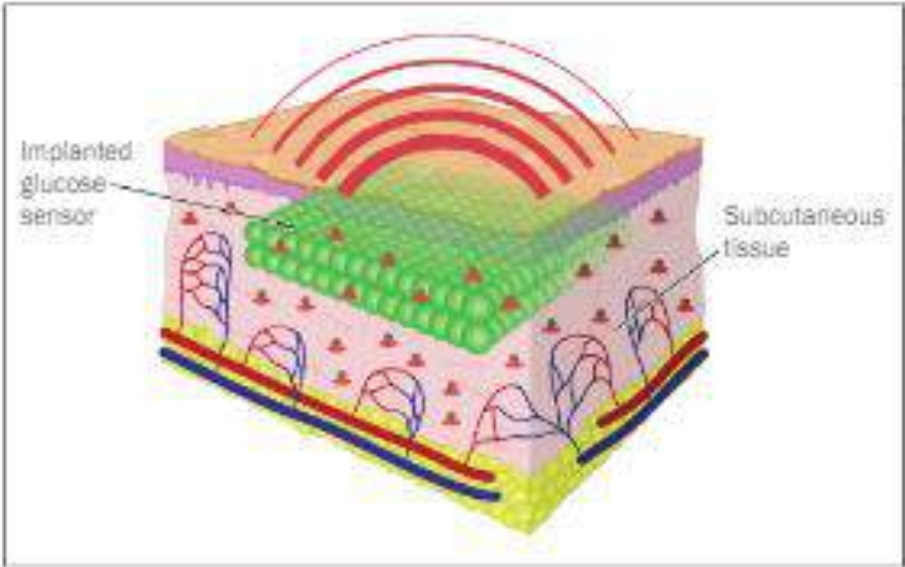
- Fast readout
- Long-term function without battery
- Susceptible to error

Amperometric



- Reliable proven technology
- Requires battery
- Frequent calibration needed

SMART TATTOO -AKILLI DÖVME-



Teşhis

- Nanoteknoloji ile Moleküler Görüntüleme ve Biyomedikal Görüntüleme etkinleşiyor
- Tip 1/Tip 2 diyabetikler için erken teşhis, evreleme ve hastalık ilerlemesinin izlenmesi için yeni fırsatlar
- Fonksiyonel β -hücrelerinin nicel tespiti
- β -hücre özgüllüğü yüksek, kontrast nanoprobalar geliştiriliyor
- Bilgisayarlı Tomografi (BT)
- Pozitron Emisyon Tomografisi (PET)
- Manyetik Rezonans Görüntüleme (MRI)***

Süperparamanyetik Demir Oksit Nanoparçacıkları (SPION'LAR)

- SPION'lar, diyabet teşhisi için erken teşhis aracı olarak
 - İmmün hücre infiltrasyonunu
 - Ardından pankreatiti
izlemek için geliştirilmiştir.

Pilot klinik çalışma;

- Yakın zamanda diyabeti olan hastalarda adacık hücre inflamasyonu sağlıklı gönüllülere göre iki kat fazla

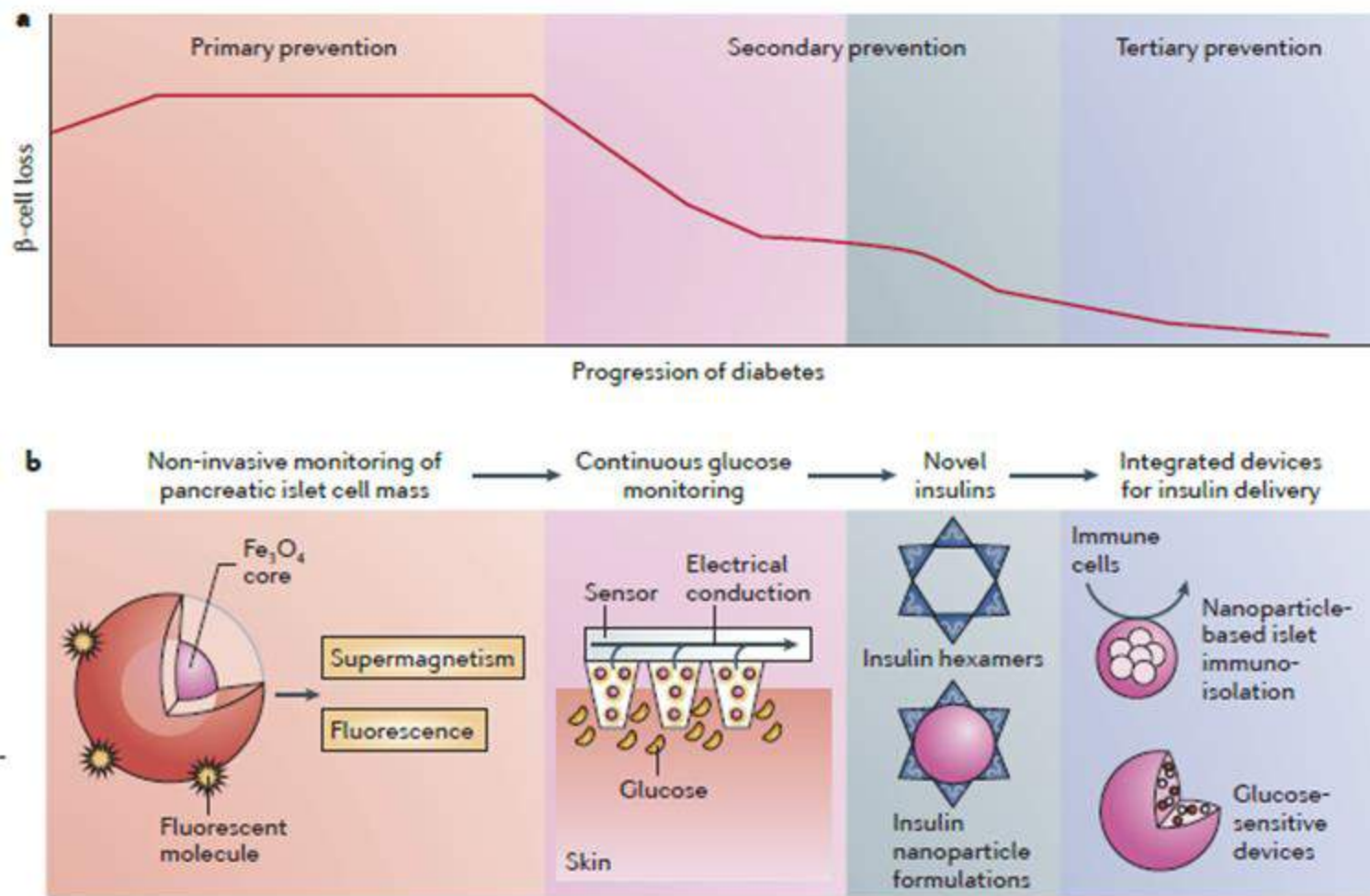
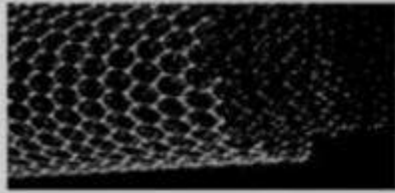
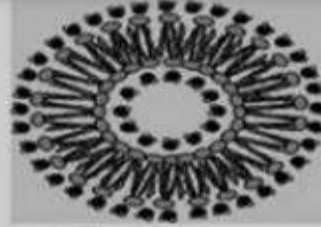


Figure 1 | Nanotechnology-based approaches to address challenges in the diagnosis and treatment of diabetes.
a | The progression of diabetes results in a loss in β -cell mass, which can be subcategorized into three stages: primary, secondary and tertiary. As the disease progresses through each stage, new types of therapies are necessary to help slow advancement to the subsequent stage. **b** | Highlighted below the profile illustrating the progressive loss in β -cell mass are potential nanotechnology-based interventions that could be developed to address patient needs at the various stages of disease progression. A number of examples are highlighted, including: nanoparticle-based contrast agents to improve early diagnosis of the onset of type 1 diabetes; nanoparticle-based continuous glucose sensors that can facilitate frequent monitoring of blood glucose levels with improved accuracy and patient comfort; nanoparticles to improve the pharmacodynamics of insulin in order to better mimic the physiological needs of the body; and nanotechnology-based protection of transplanted pancreatic islet cells. These approaches can be used as highlighted to help maintain healthy normoglycaemic levels in patients with diabetes.

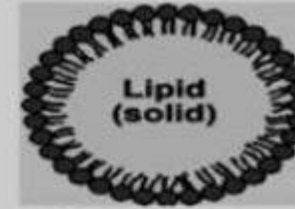
NANOPARTİKÜL İLAÇ DAĞITIM SİSTEMLERİ



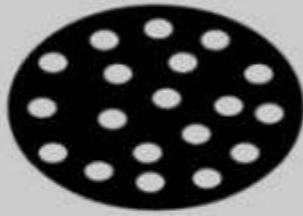
(a) nanotubes



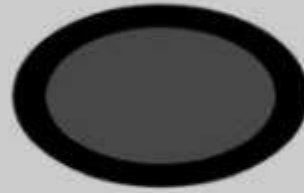
(b) liposomes



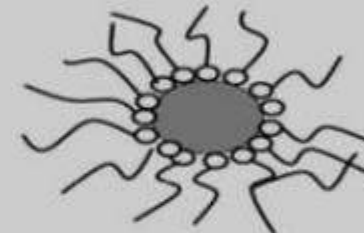
(c) SLN



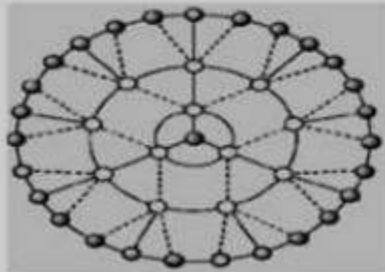
d (i) nanospheres



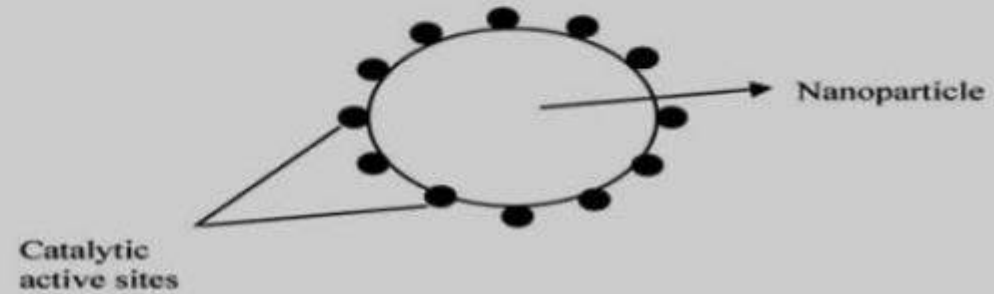
d (ii) nanocapsules



(e) Polymeric micelles



(f) dendrimers



(g) functionalized nanoparticles

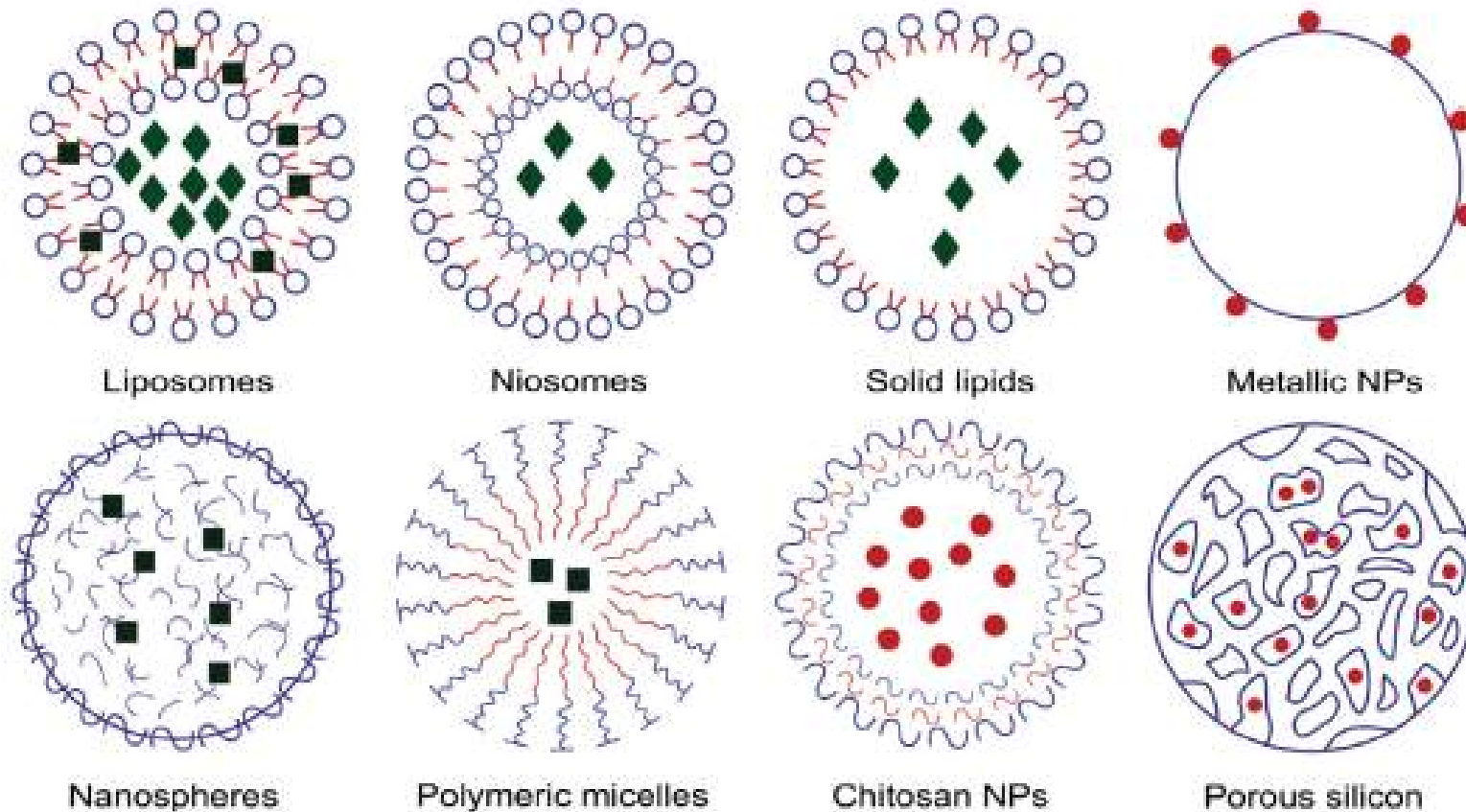
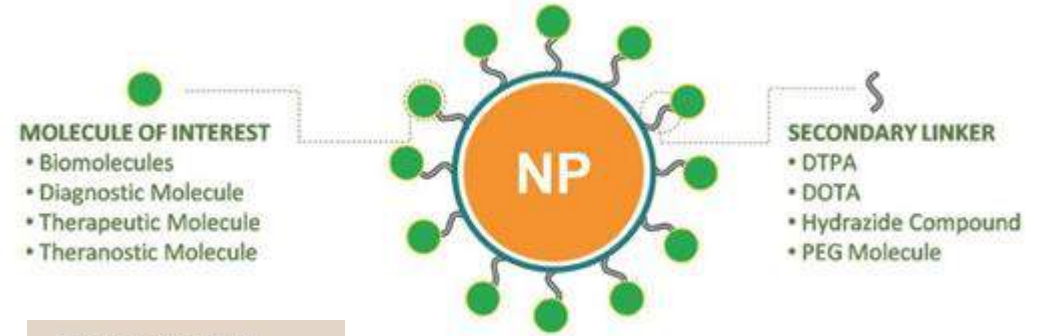


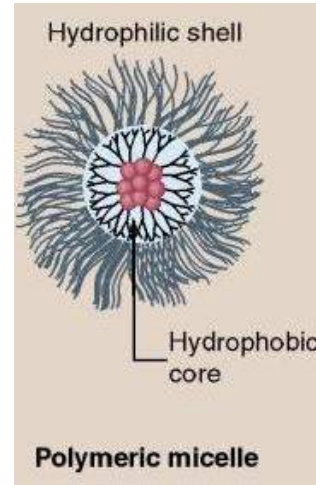
Fig. 1 - An overview of the different nanocarriers used for the delivery of anti-diabetic drugs. In brief, liposomes are small spherical vesicles created from cholesterol and non-toxic phospholipids. Niosomes are multilamellar vesicular structures of non-ionic surfactants. Solid lipids are made of solid lipids or lipid blends. Metallic NPs are nanosized metals that can easily conjugate with various biological agents. Nanospheres are matricial nanostructures of spherical shapes (usually polymeric); Polymeric micelles are core/shell structures formed by amphiphilic block copolymers. Chitosan NPs are NPs formed by the incorporation of a polyanion (e.g. such as tripolyphosphate) with chitosan. Porous silicon NPs are hollow NPs made of porous silicon.

İnsülin İletimi

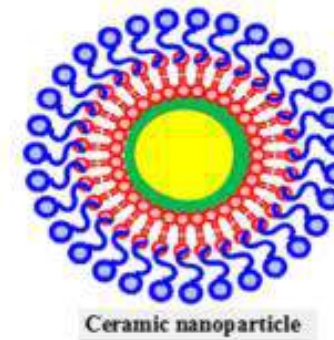
1. Polimerik biyolojik olarak parçalanabilen nanoparçacıklar



2. Polimerik miseller

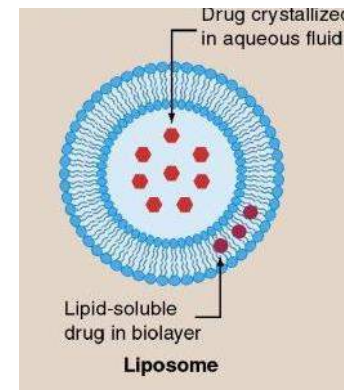


Functional nanoparticles

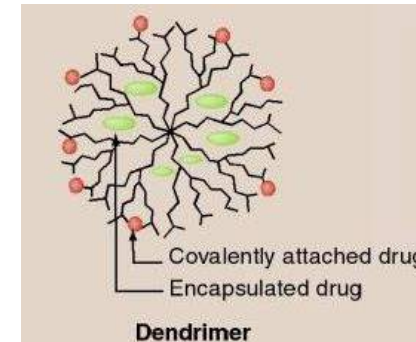


3. Seramik nanoparçacıklar

4. Lipozomlar



5. Dendrimer



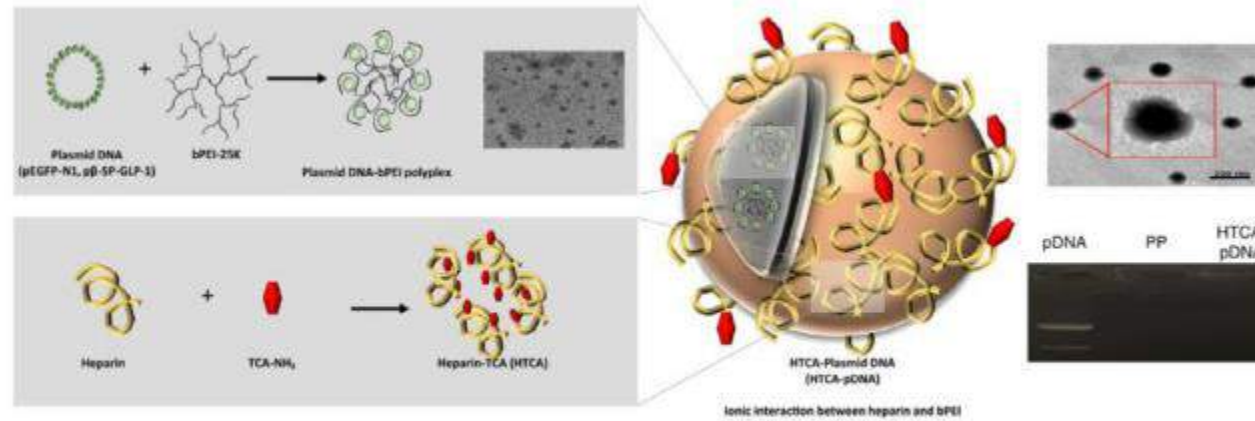


Fig. 5 – Synthesis of the Heparin-Taurocholic acid (HTCA))-GLP1.

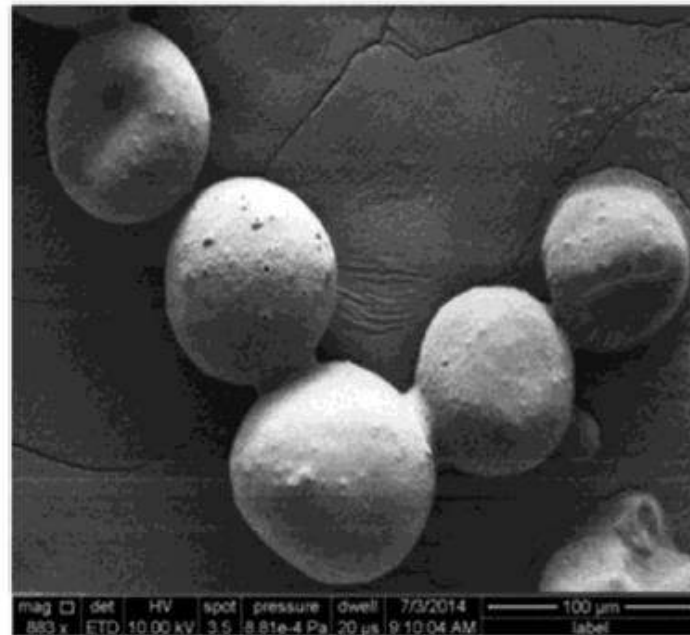


Fig. 6 – Scanning electron microscopy image of the H-PGLA particles.
2016 The Royal Society of Chemistry.

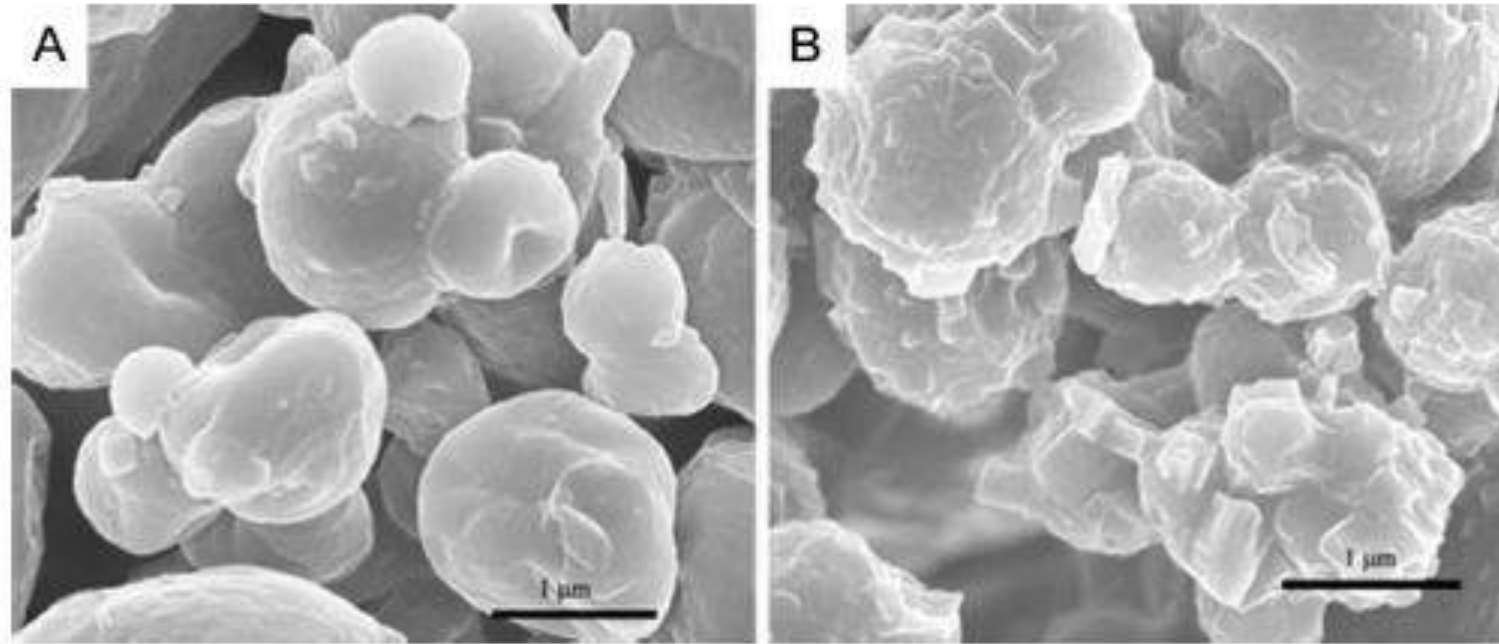


Fig. 9 – Scanning electron microscopy images of (A) CS-coated liposomes and (B) β -glycerolphosphate /CS microcomplexes.
Copyright 2013 Springer Nature.

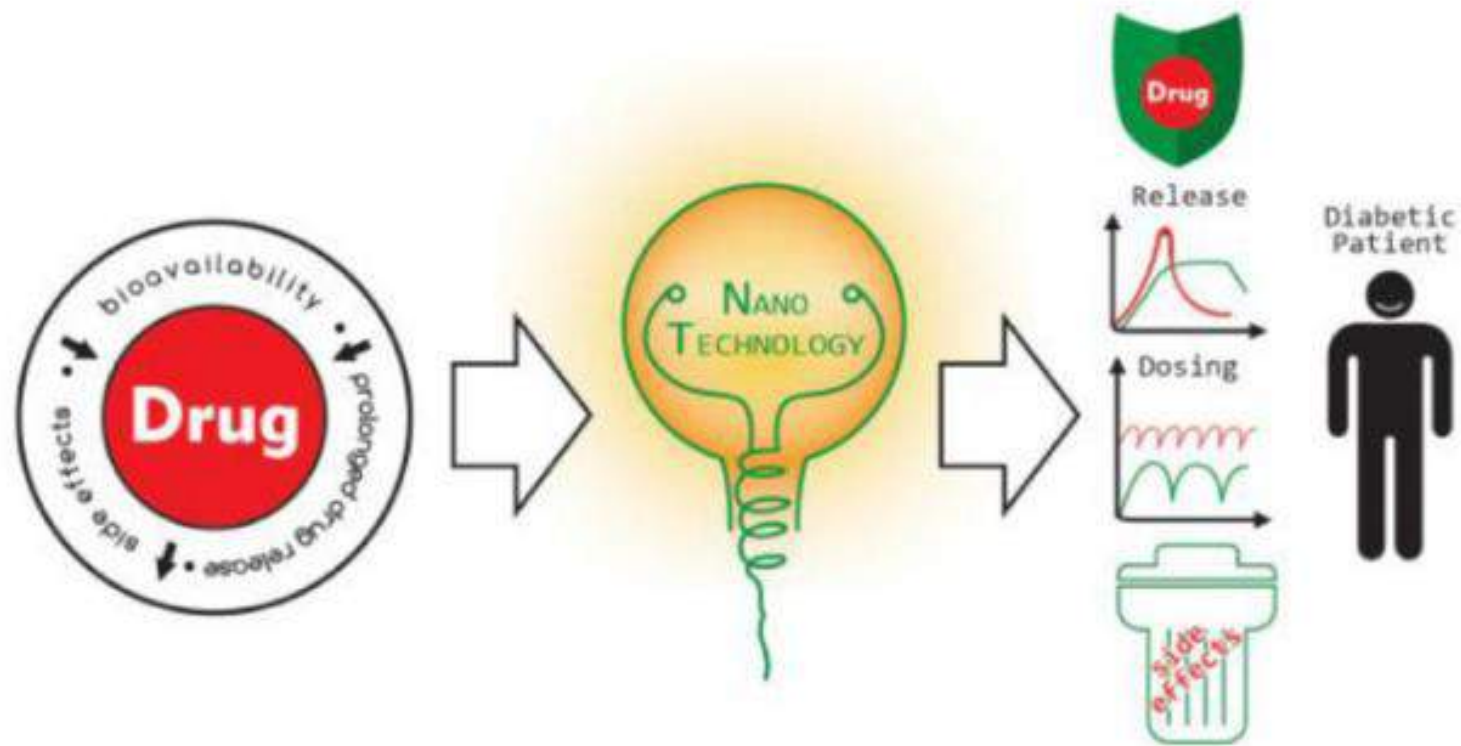


Fig. 2

Nanotechnology approach in T2DM treatment.

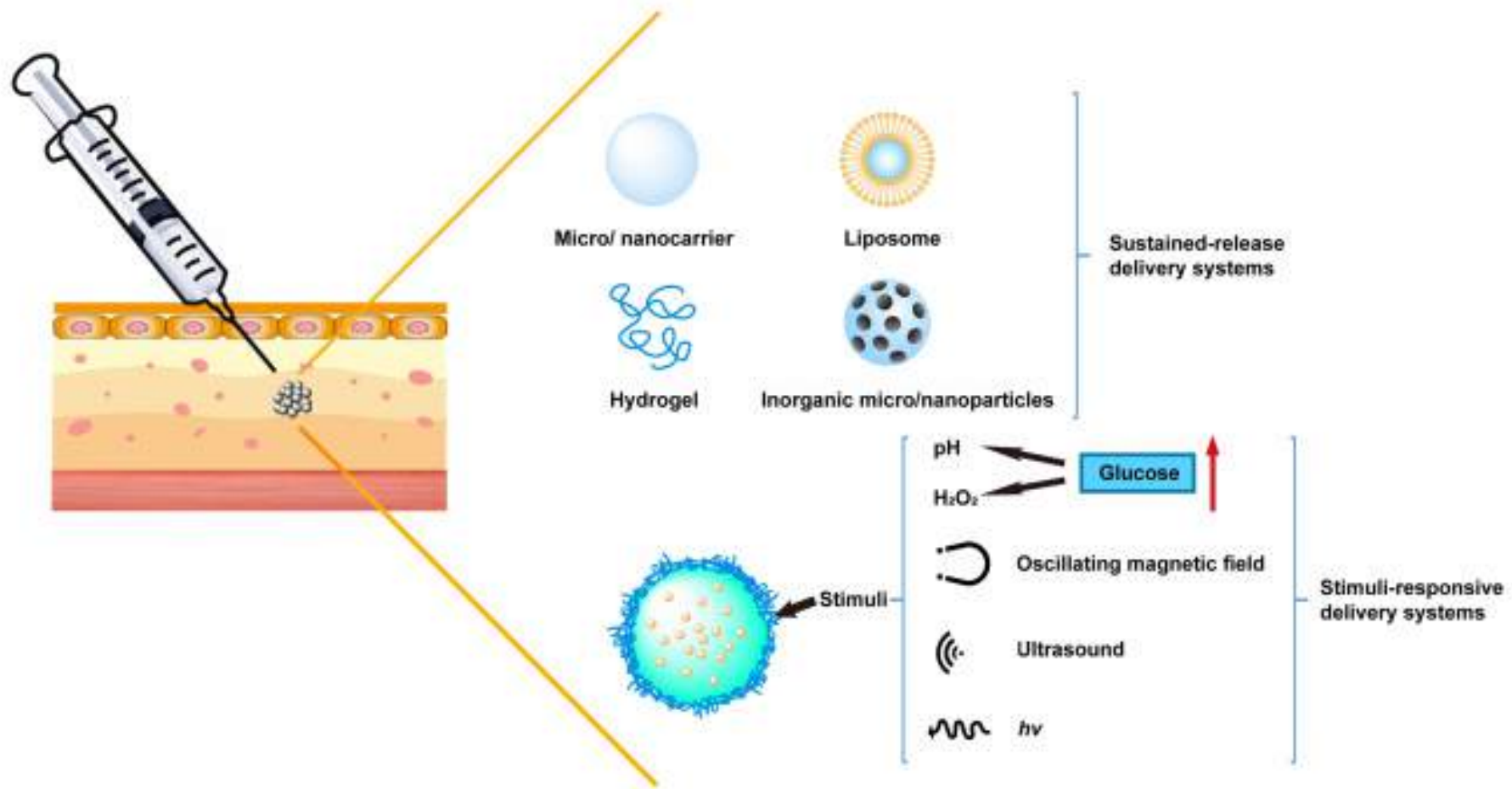
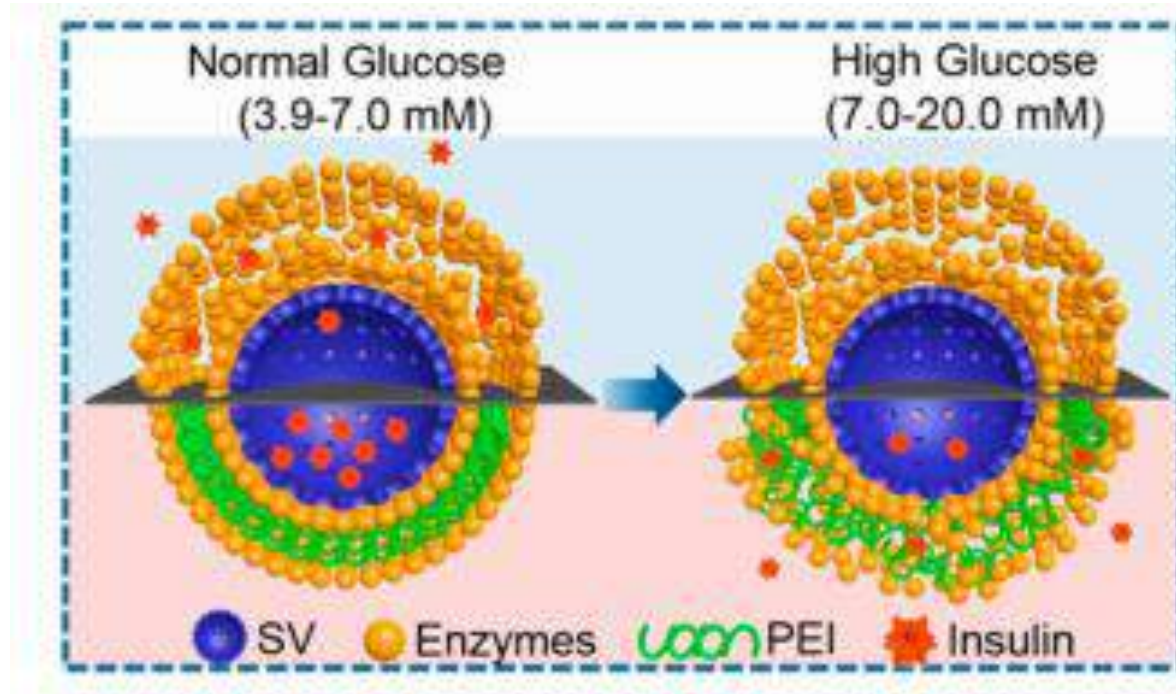


Figure 2 Schematic illustration of various subcutaneous delivery systems used for antidiabetic biomacromolecular drugs.

Fizyolojik Glikoz Duyarlı Sistem -Farklı İnsülin Salınım Durumları-



Xu C et al. Chemistry of Materials. 2017;29(18):7725–7732

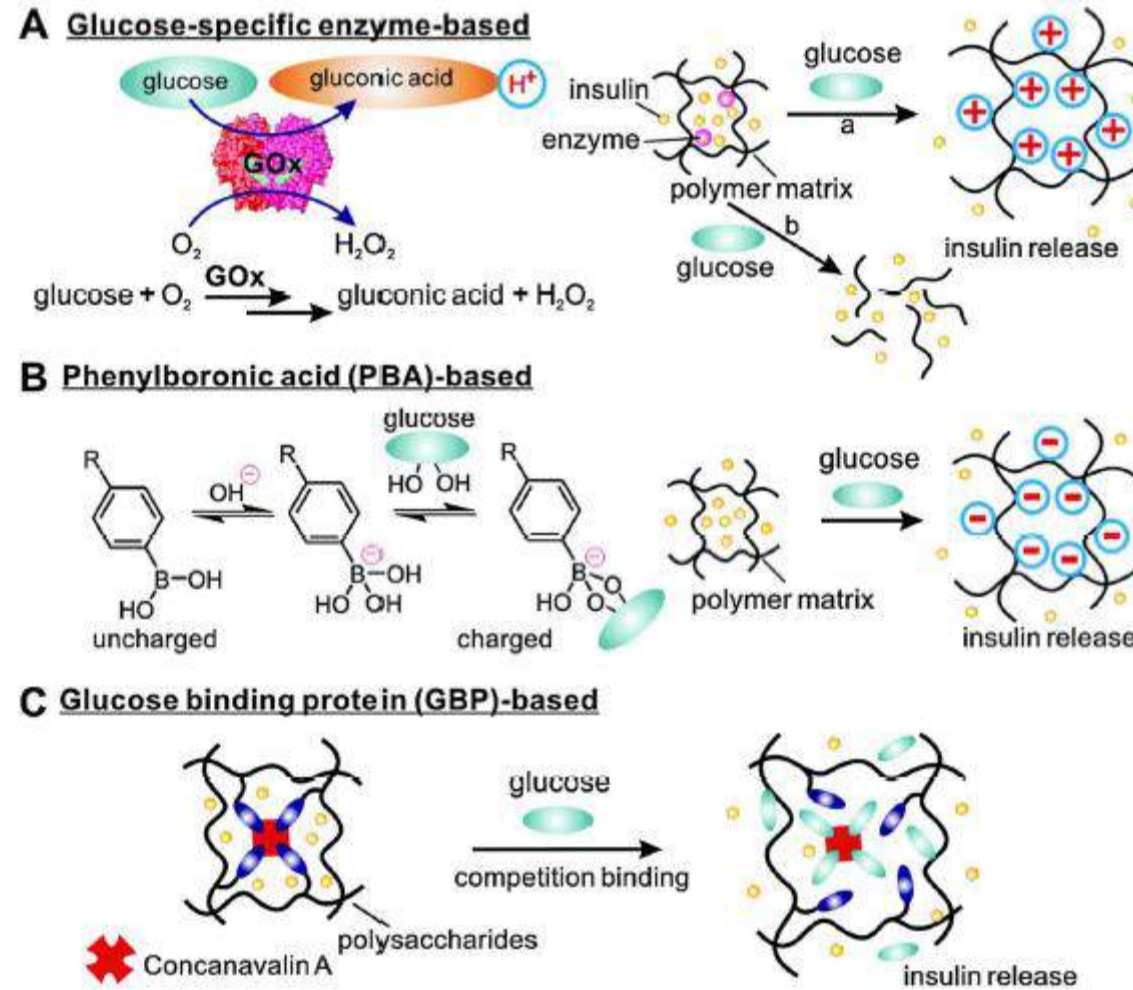
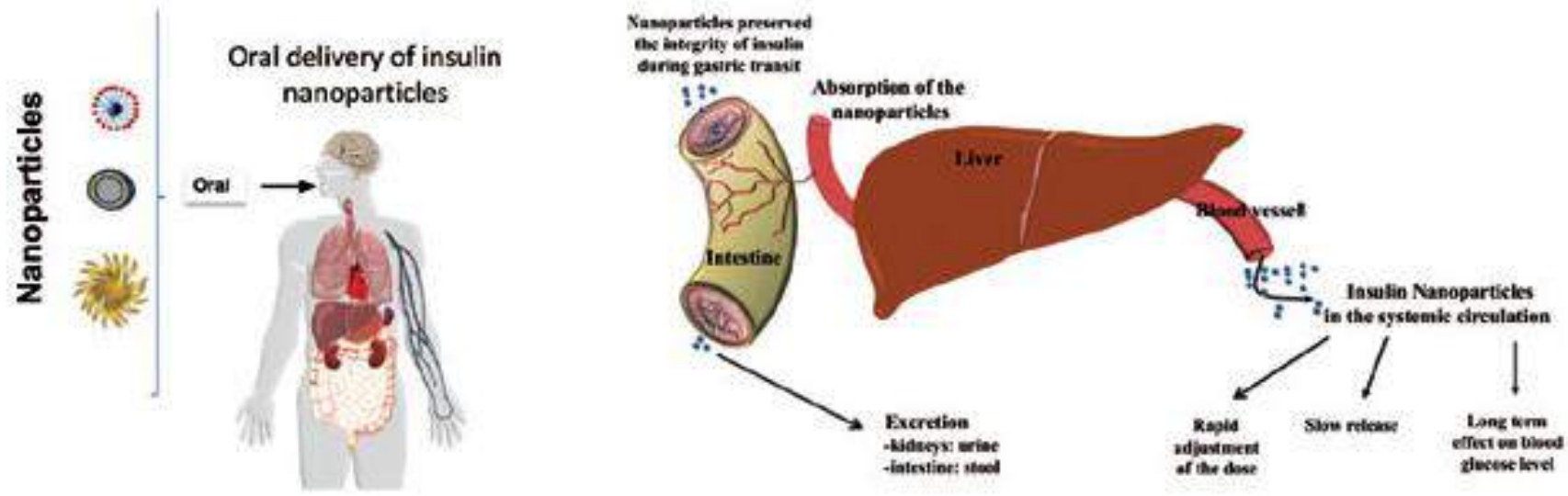


Figure 6. Schematic of typical strategies for glucose responsive insulin release.

Oral İnsülin



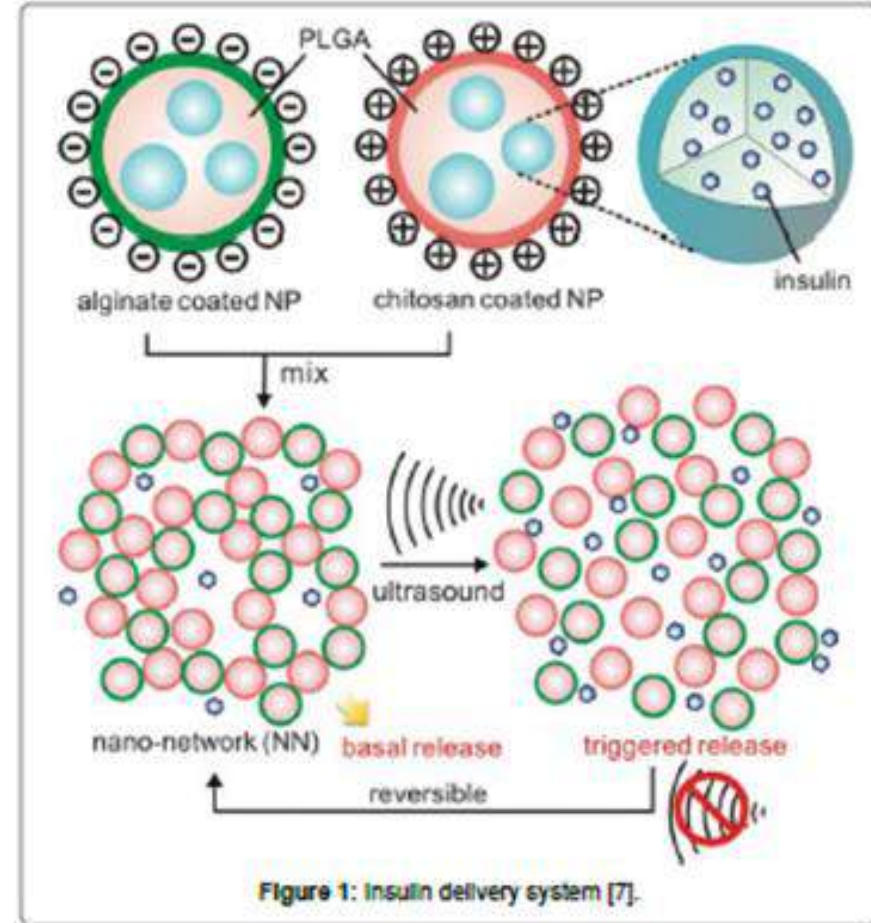
Behman F et al. Pharmaceutical Nanotechnology, 2019, 7, 113-128

*Nanopartiküller sayesinde inhaler insülin de mümkündür

Simos YV et al. Asian Journal of Pharmaceutical Sciences 16 (2021) 62–76

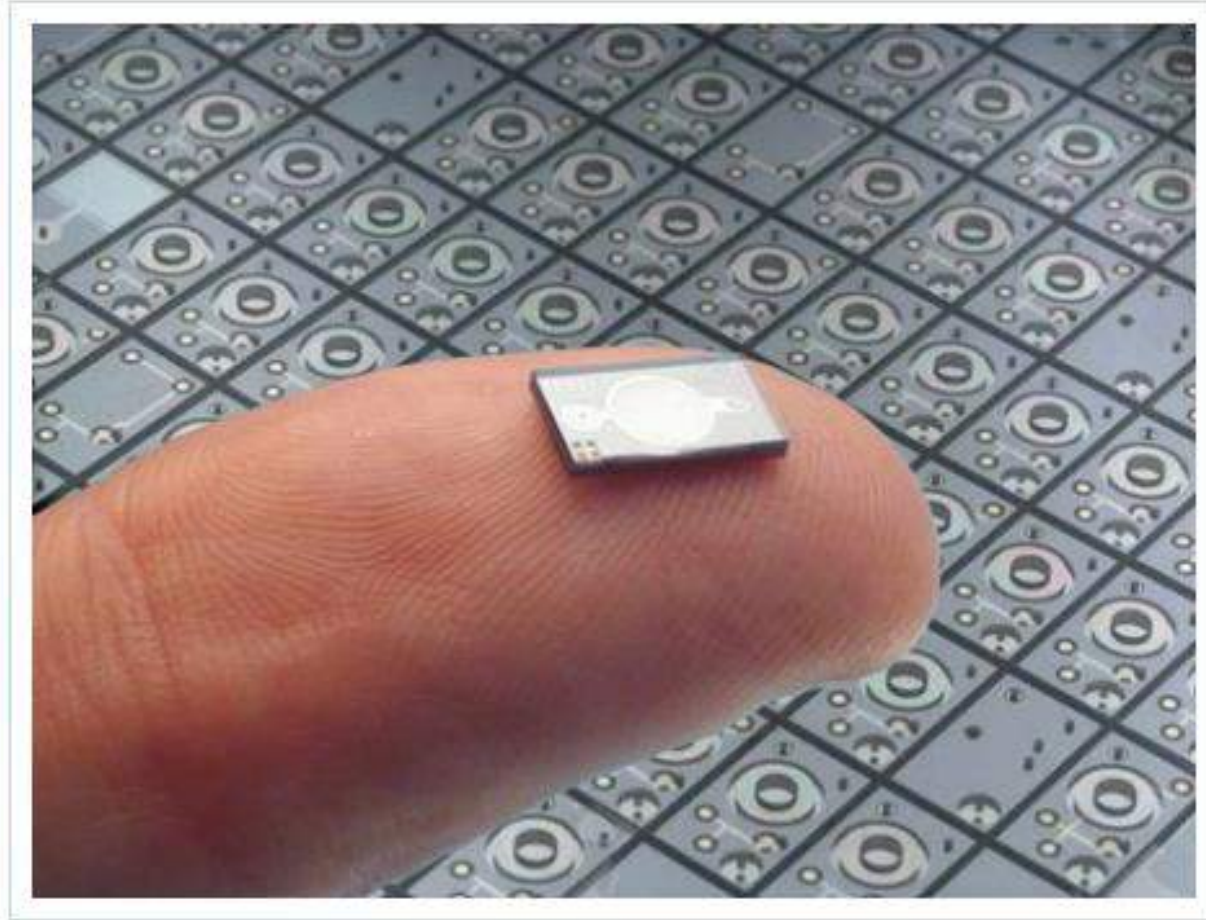
Oral ve İnhaler İnsülin

- Hayvan çalışmalarında **oral yol**;
- İnsülin yüklü polimerik nanopartiküllerin verilmesi için mikropelletler
- Mikroküreler, insülini etkili bir şekilde taşır;
- Hem proteaz inhibitörü
- Hem de geçirgenlik arttırıcı olarak işlev görür
- **İnhaler insülin** için çitosan nanoparçacıkları
- Potansiyel en uygun sistem



Nano Pompalar

- Sürekli Deri Altı İnsülin İnfüzyonu-



AKILLI İNSULİN BANTLARI



Figure 2: Smart insulin patch [10].

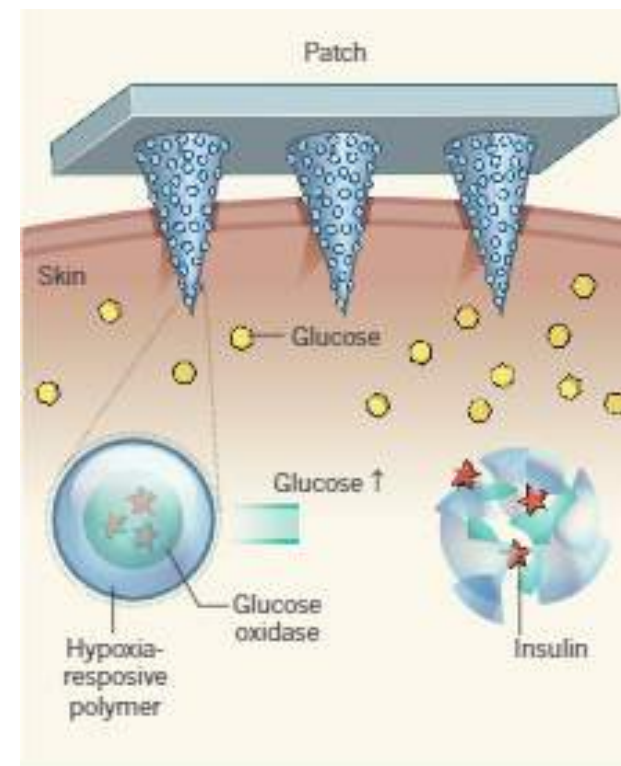


Figure 1 | A microneedle patch to monitor glucose and release insulin. Yu *et al.*⁴ have developed a smart insulin-releasing patch made of 121 nanoparticle-containing microneedles. The patch painlessly penetrates the interstitial fluid between subcutaneous skin cells. The nanoparticles in each needle contain insulin and the glucose-sensing enzyme glucose oxidase, which converts glucose to gluconic acid. These molecules are surrounded by a hypoxia-responsive polymer. Increases in glucose oxidase activity in response to glucose elevation produce a low-oxygen environment in the nanoparticles, which is sensed by the hypoxia-responsive polymer, triggering disassembly of the nanoparticles and the release of insulin.

Kapalı Döngü İnsülin Sistemleri

-Yapay Pankreas=Bionik Pankreas-

- Sürekli Bir Glikoz Monitörü
 - Glikoz Ölçer
 - İnsülin İnfüzyon Pompası
- Yapay Pankreas Sistemi
- Hassas nano-sensörler
 - Glikoz sensör fonksiyonunu iyileştiren nanomalzemeler
 - Çeşitli nanoteknolojik sistemlerle insülinin uygulanması
 - Glukagon hipoglisemi riskini azaltmak için birlikte verilebilir

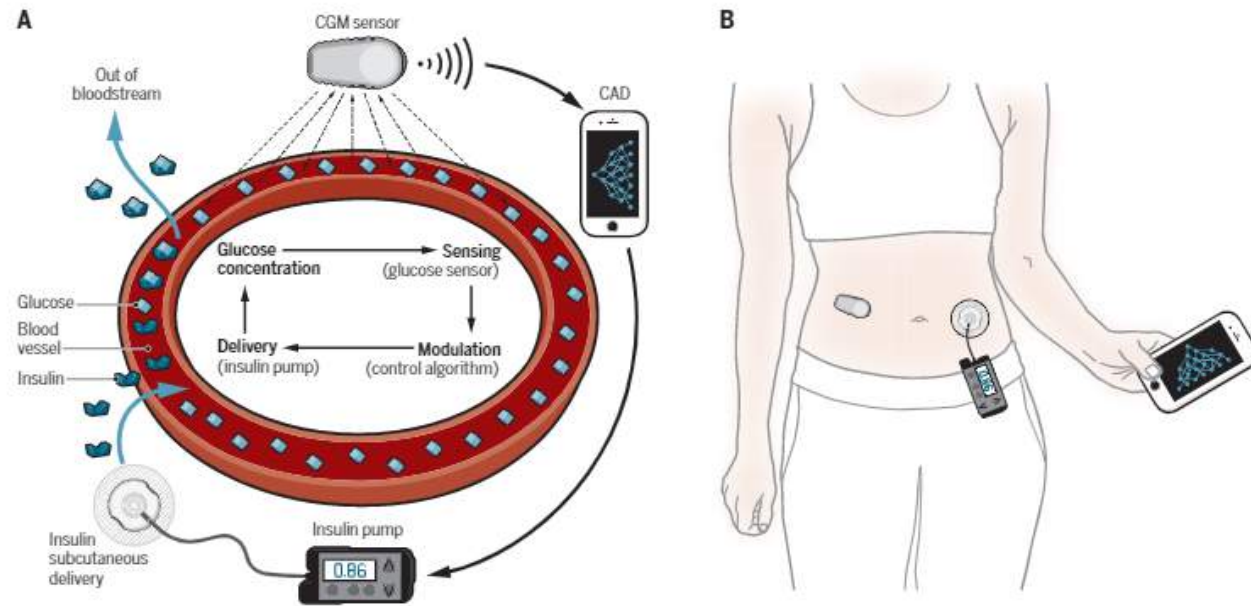
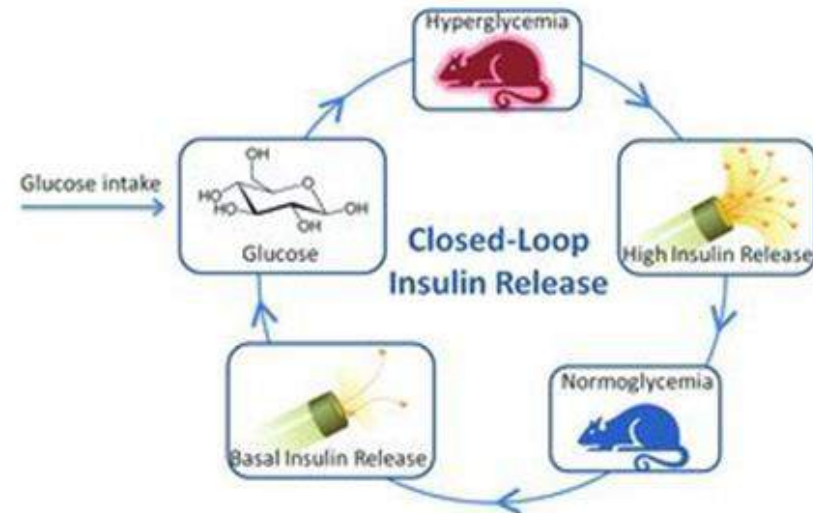


Fig. 1. Closed-loop artificial pancreas systems. (A) Diagram depicting closed-loop insulin delivery. A continuous glucose monitor (CGM) worn subcutaneously transmits information about interstitial glucose concentrations to a smartphone or other control algorithm device (CAD), which hosts a control algorithm that translates information from the CGM and computes the amount of insulin to deliver. An insulin pump delivers rapid-acting insulin analog subcutaneously. Insulin delivery is modulated in real time by the control algorithm. Communication between system components is wireless. (B) Schematic depicting where the components of a closed-loop insulin delivery system may be worn and held by a human subject with type 1 diabetes.

Boughton and Hovorka, *Sci. Transl. Med.* 11, eaaw4949 (2019)



Gordiojo CR et al. *Advanced Functional Materials*, (2011) 21, 73-82

Real-Time Glikoza Duyarlı İnsülin Salınımı için Subkutan İmplant

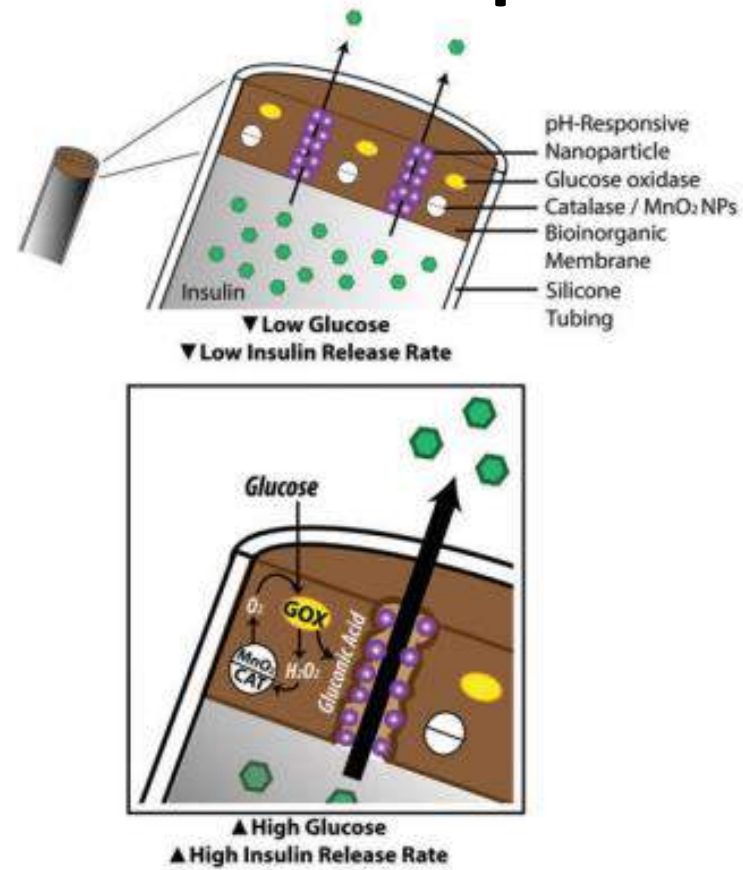


FIG. 1. Schematic for glucose-responsive insulin micro-devices: **(top)** polydimethylsiloxane (silicone) tubing microdevice with a bioinorganic plug and the cross-section of the device with embedded hydrogel nanoparticles (NPs) and **(bottom)** cross-sectional diagram of the membrane response to glucose at high glucose concentrations. CAT, catalase; GOX, glucose oxidase. (A color graphic is available online at www.liebertonline.com/dia)

Glikoz Aracılı İnsülin Salınımı için Enjekte Edilebilir Nano Network

- Enjekte edilebilir insülin içeren nanopartiküler jeller
- Nanopartiküller, vücuttaki glikoz seviyelerini algılar
- Her nanoparçacık, glikozu glukonik aside dönüştüren Glukoz oksidaz yüklü dekstran küreleri içerir
- Glikoz jel içerisinde serbestçe dağılır
- Kan şekeri yükselince glukonik asit üretilir, ortamı tam asidik olur
- Asidik ortam, dekstran kürelerinin parçalanmasına ve insülin salmasına neden olur.
- Tip 1 diyabetli farelerde jelin tek bir enjeksiyonunu ortalama 10 gün boyunca normal kan şekeri seviyelerini korur

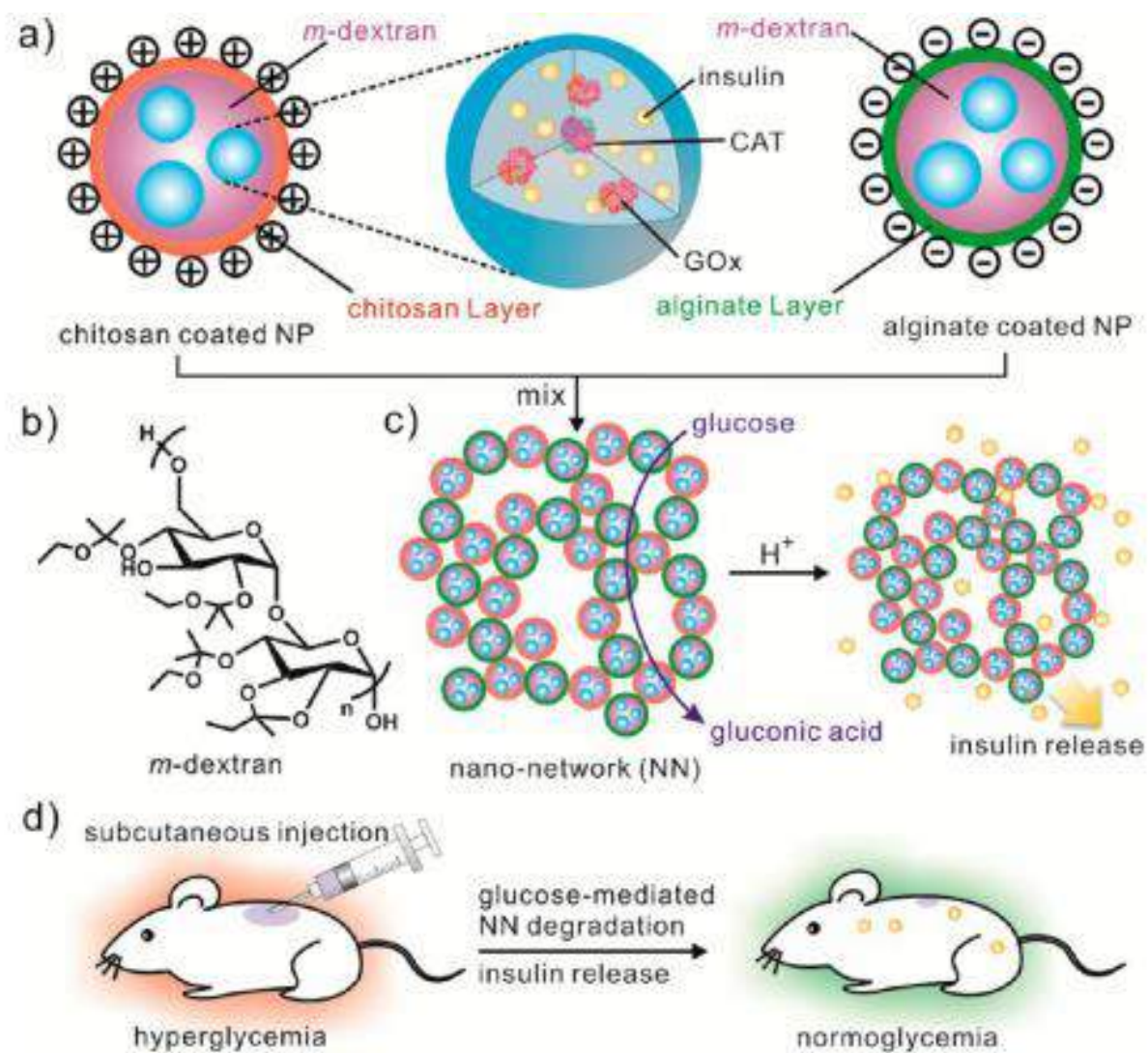


Figure 1. Schematic of the glucose-responsive nano-network. (a) Nanoparticles (NPs) encapsulating insulin and glucose-specific enzymes (GOx, glucose oxidase; CAT, catalase) are made of acidic sensitive acetal-modified dextran (b) and coated with chitosan and alginate, respectively. (c) Nano-network (NN) is formed by mixing oppositely charged nanoparticles together and efficiently degrades to release insulin upon the catalytic generation of gluconic acid under hyperglycemic conditions. (d) Schematic of glucose-mediated insulin delivery for type 1 diabetes treatment using the STZ-induced diabetic mice model.

Yapay Zeka ile İşler Kolaylaşacak...

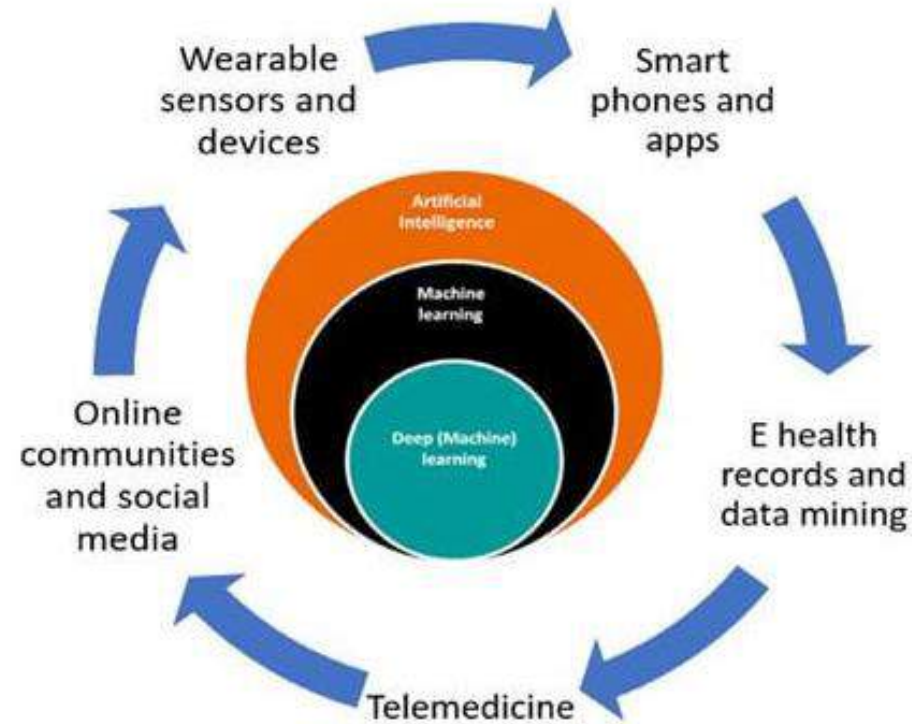


Figure 2 Applications of artificial intelligence in diabetes care.

GLP-1 ve Nanoteknoloji

- Nanosistemler, GLP-1'in oral yoldan verilmesi için kullanılabilir ve onu bozulmadan aktif olarak korur.
- Kaplı nanosistemler peptit salınımını da uzatır.
- GLP-1 bazlı nanomalzemeler/nano-DPP4 inhibitör taşıyıcıları GLP-1'in uzun süreli aktivasyonunu sağlar

İnsülin Dışı Antidiyabetikler ve Nanoteknoloji

GLP-1

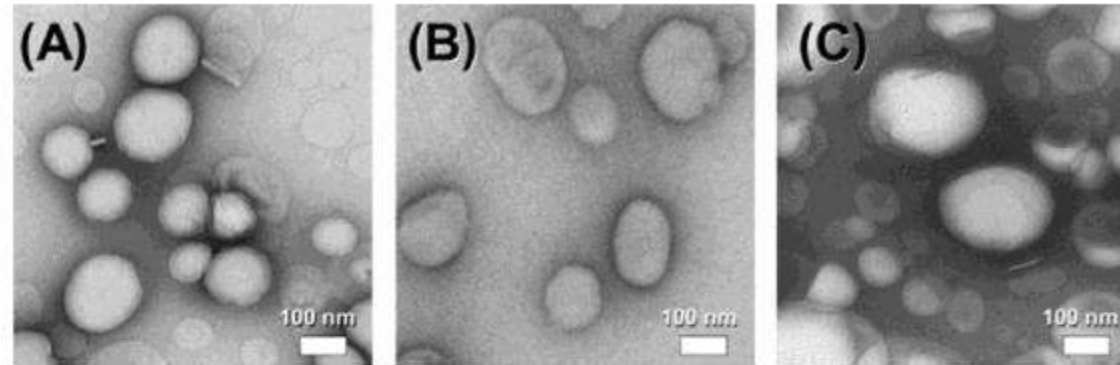


Fig. 3 – Representative transmission electron microscopy images of the (A) anionic, (B) nonionic and (C) cationic CLP-1 formulations. Reprinted with permission from [51]. Copyright 2009 Elsevier B.V.

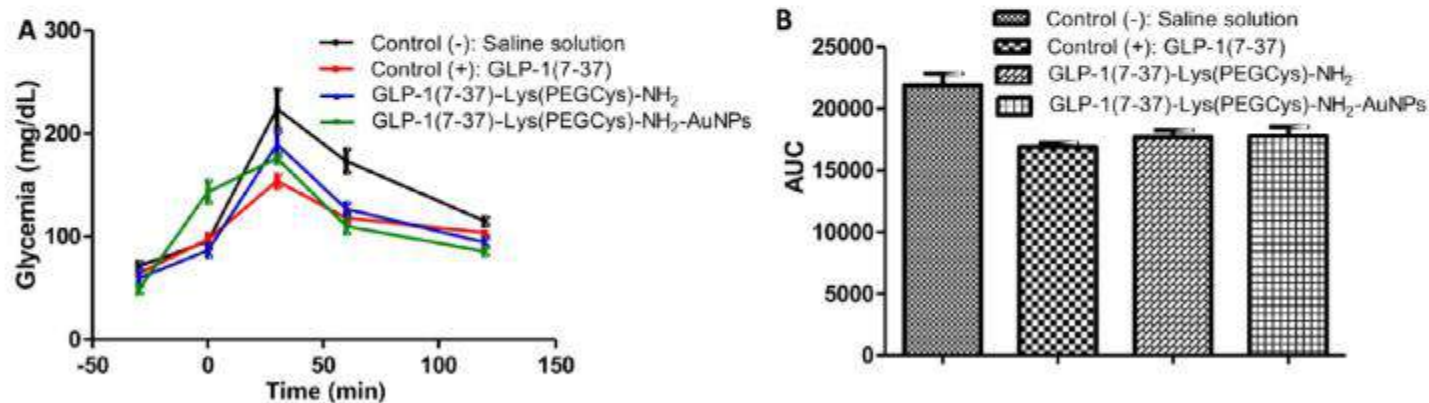


Fig. 4 – (A) Blood glucose response after loading with 2 g/kg glucose and treatment with saline solution, GLP-1(7-37), GLP-1(7-37)-Lys(PEGCys)-NH₂ and GLP-1(7-37)-Lys(PEGCys)-NH₂ conjugated to AuNPs and (B) AUC obtained after data analysis from Fig. 5. Reprinted with permission from [55]. Copyright 2016 Elsevier B.V.

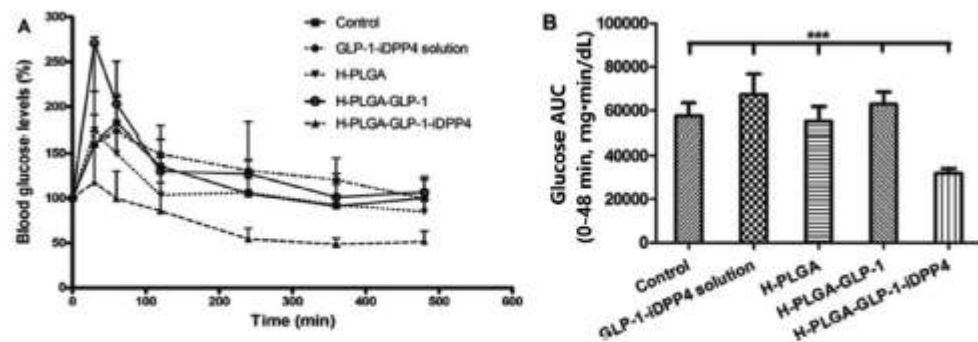


Fig. 7 – (A) Glycemic profile of T2DM-induced rats after oral administration of phthalate buffer solution (control), GLP-1 iDPP4 solution, H-PGLA particles, H-PGLA-GLP-1 particles and H-PGLA-GLP-1 iDPP4 particles and (B) AUC for a period of 6 h after oral administration. **P < 0.001, as compared with the H-PGLA-GLP-1 iDPP4.

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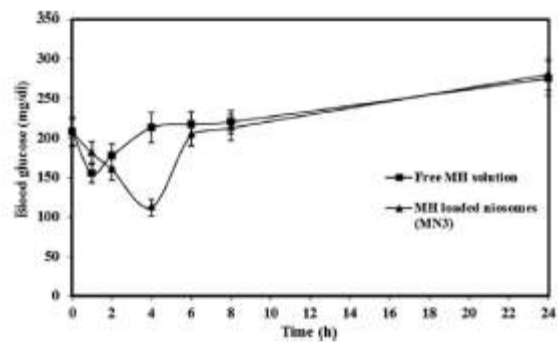


Fig. 8 – Effects of the free MH solution or MH loaded niosomes on blood glucose levels of STZ-induced diabetic rats.

Taylor and Francis.

Nano Teknolojinin Kullanıldığı Diğer İlaçlar

- **Gliklazid;** niozomlar ile ilacın dolaşıma sürekli salınımı sağlanır
- Gliklazid salınımını uzar ve hipoglisemik aktivitesini artır
- **Metformin;** niozomlar kullanılabilir
- İlaç salınımı uzar ve etki artır
- **Pioglitazon ve Repaglinid;** nano-formülasyonları yapıldı ve daha etkili bulundu
- **Eksenatid;** nano formları ile oral verilebilir ve etkisi subkutan formlardan daha uzun olur
- **Vildagliptin;** nano formüller, normal formulasyona göre daha uzun etkili

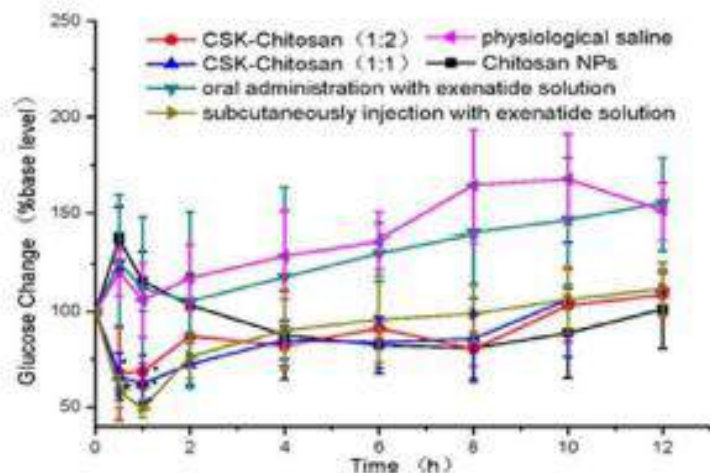


Fig. 10 – Glycemic profile of diabetic rats following the oral administration of CS-NPs, CSK-CS (1:1) NPs, CSK-CS(1:2) NPs (30.0 µg/kg exenatide), exenatide solution (7.5 µg/kg), physiological saline and SC injection with exenatide solution (5.0 µg/kg).

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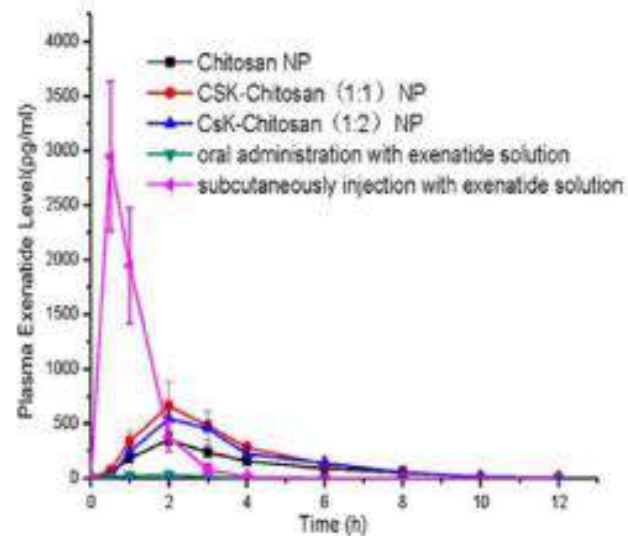
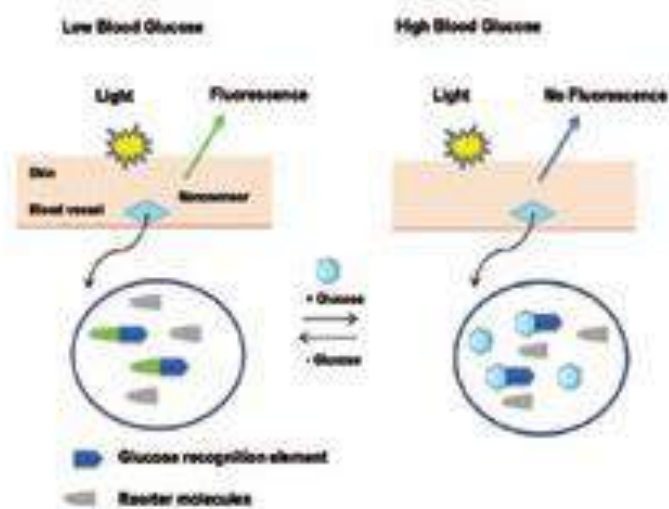


Fig. 11 – Plasma exenatide level in diabetic rats following the oral administration of CS-NPs, CSK-CS (1:1) NPs, CSK-CS(1:2) NPs (30.0 µg/kg exenatide), exenatide solution (50 IU/kg), with SC injection with exenatide solution (5.0 IU/kg) used as positive control.

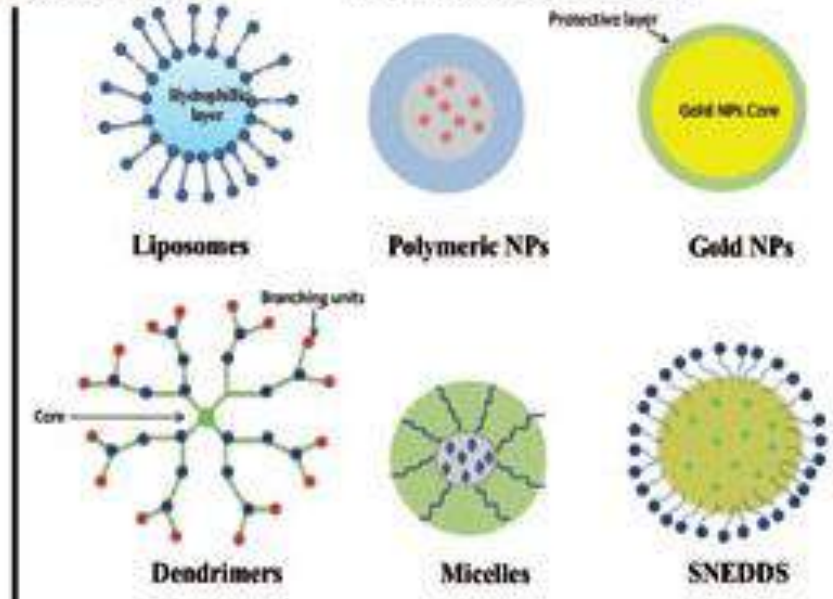
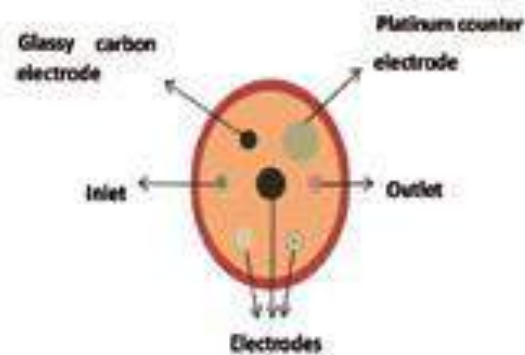
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Detection of insulin/ BGL ← **Nanotechnology in management of DM** → **Nanocarriers employed as antidiabetic DDS**

1-Implantable Sensor



2- Microphysiometer



Applications

1. Oral Insulin
2. Inhalable NPs
3. Artificial Pancreas Device System
4. Nanopump



Artificial Pancreas Device System

Yapay Zeka

- Bilgiyi analiz eden sistemler ve metodlar oluşturmayı amaçlayan
- Çok çeşitli uygulamaların derinliğinde karmaşıklığın çözülmesini sağlayan bir bilgisayar bilim dalıdır
- 1950'lerde geliştirildi...

Ancak bunu mümkün kılmak için;

- Bilgi işlem gücündeki ilerlemeler
- “Büyük Veri” patlaması
- Bugün popüler hale geldi
- **Yapay zeka**; akıllı makineler ve programlar yapma mühendisliğidir

Yapay Zeka (YZ) ve Diyabet



Yapay zekanın diyabete uygulanması mümkün ve arzu edilir bir durumdur

Diyabet Bakımında Kullanılabilen Teknikler

- **Vaka Bazlı Çözümleme:** Benzer geçmiş olaylardan öğrenmeye dayalı yeni sorunları çözmek için bir YZ tekniğidir, diyabet yönetiminde yaygın olarak kullanılmaktadır.
- **Makine Öğrenimi ve Derin Öğrenme:** Diyabet bakımında dijital destek oluşturmak için çeşitli makine öğrenimi süreçleri kullanılmıştır.
 - Support Vector Machine
 - Artificial Neural Network
 - Naïve Bayes
 - Decision Tree
 - Random Forest
 - Classification And Regression Trees
 - K-nearest Neighbor

Application of support vector machine modeling for prediction of common diseases: the case of diabetes and pre-diabetes

Wei Yu¹, Tiebin Liu, Rodolfo Valdez, Marta Gwinn, Muin J Khoury

Abstract

Background: We present a potentially useful alternative approach based on support vector machine (SVM) techniques to classify persons with and without common diseases. We illustrate the method to detect persons with diabetes and pre-diabetes in a cross-sectional representative sample of the U.S. population.

Methods: We used data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES) to develop and validate SVM models for two classification schemes: Classification Scheme I (diagnosed or undiagnosed diabetes vs. pre-diabetes or no diabetes) and Classification Scheme II (undiagnosed diabetes or pre-diabetes vs. no diabetes). The SVM models were used to select sets of variables that would yield the best classification of individuals into these diabetes categories.

Results: For Classification Scheme I, the set of diabetes-related variables with the best classification performance included family history, age, race and ethnicity, weight, height, waist circumference, body mass index (BMI), and hypertension. For Classification Scheme II, two additional variables—sex and physical activity—were included. The discriminative abilities of the SVM models for Classification Schemes I and II, according to the area under the receiver operating characteristic (ROC) curve, were 83.5% and 73.2%, respectively. The web-based tool-Diabetes Classifier was developed to demonstrate a user-friendly application that allows for individual or group assessment with a configurable, user-defined threshold.

Conclusions: Support vector machine modeling is a promising classification approach for detecting persons with common diseases such as diabetes and pre-diabetes in the population. This approach should be further explored in other complex diseases using common variables.

BMC Medical Informatics and Decision Making (2010),10:1;16

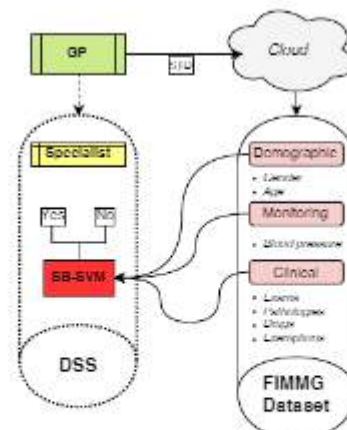


Fig. 1: Overview of the Decision Support System (DSS) architecture emerging from the SB-SVM approach. The General Practitioner (GP) stores the EHR data in Netmedica Italia (NMI) Cloud platform. The FIMMG dataset is composed of three different fields: demographic, monitoring and clinical. The related features were used for training the SB-SVM model and providing a T2D prediction.

Support Vector Machine

JOURNAL OF IEEE BIOMEDICAL AND HEALTH INFORMATICS

Discovering the Type 2 Diabetes in Electronic Health Records using the Sparse Balanced Support Vector Machine

Michele Bernardini, Luca Romeo, Paolo Misericordia, and Emanuele Frontoni, *Senior Member, IEEE*,

Abstract—The diagnosis of Type 2 Diabetes (T2D) at an early stage has a key role for an adequate T2D integrated management system and patient's follow-up. Recent years have witnessed an increasing amount of available Electronic Health Record (EHR) data and Machine Learning (ML) techniques have been considerably evolving. However, managing and modeling this amount of information may lead to several challenges such as overfitting, model interpretability and computational cost. Starting from these motivations, we introduced a ML method called Sparse Balanced Support Vector Machine (SB-SVM) for discovering T2D in a novel collected EHR dataset (named FIMMG dataset). In particular, among all the EHR features related to examinations, examination and drug prescriptions we have selected only those collected before T2D diagnosis from a

subset of subjects. We demonstrated the reliability complications [2]. Moreover, diabetes is the major cost on the economic balances of national health systems (IDF indicates for the year 2015 a level of expenditure for the treatment of diabetic patients equal to 11.6% of the total world health expenditure).

A more efficient integrated management system, including General Practitioners (GPs) and specialists with multidisciplinary skills, could be a valid solution to alleviate the healthcare costs while preventing diabetes-related diseases (e.g., diabetic retinopathy, renal diabetes). Almost all GP outpatient clinics are now equipped with EHRs storing the health history of the patients as well as several heterogeneous information (i.e. demographic, monitoring, lifestyle, clinical).

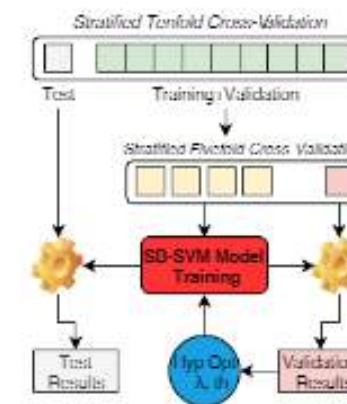


Fig. 2: Overview of the SB-SVM model architecture. A Tenfold Cross-Validation procedure was executed. The optimization of the SB-SVM hyperparameters was performed implementing a grid-search and optimizing the macro-recall score in a nested stratified Fivefold Cross-Validation. Hence, each split of the outer loop was trained with the optimal hyperparameters tuned in the inner loop.

Artificial Neural Network



Deep Learning Techniques for Biomedical and Health Informatics

2020, Pages 327-339



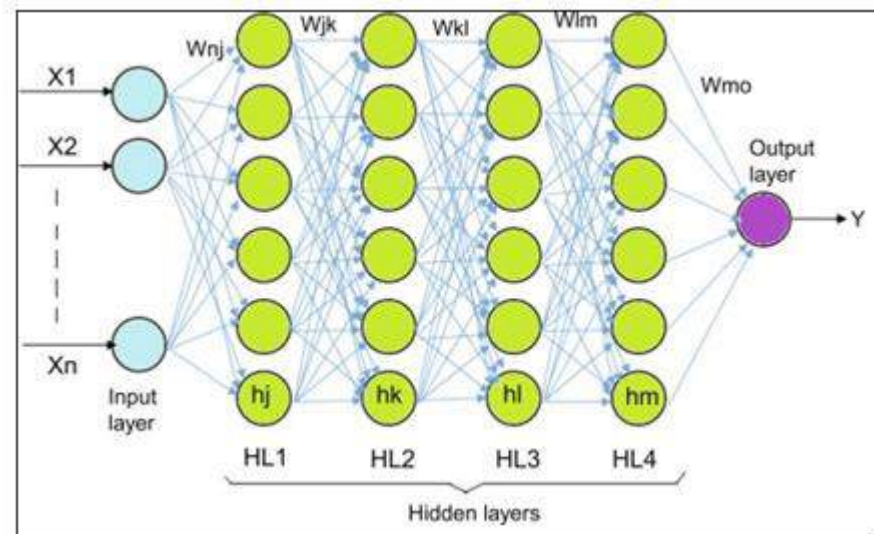
Expert Systems with Applications

Volume 39, Issue 1, January 2012, Pages 54-60



14 - Diabetes prediction using artificial neural network

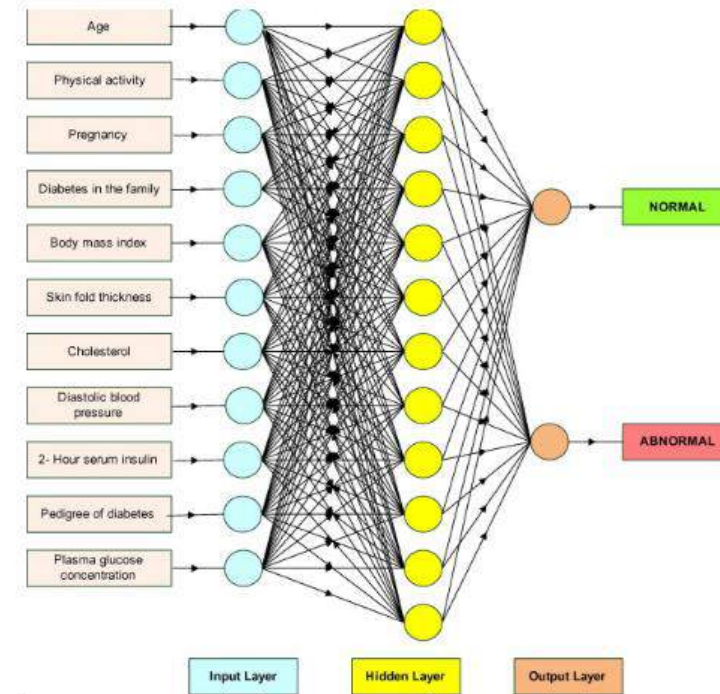
Nitesh Pradhan ^a, Geeta Rani ^a, Vijaypal Singh Dhaka ^a, Ramesh Chandra Poonia ^b



Deep Learning Techniques for Biomedical and Health Informatics (2020), 327-339

Diagnosing diabetes using neural networks on small mobile devices

Oğuz Karan ^a, Canan Bayraktar ^a, Haluk Gümüşkaya ^b, Bekir Karlık ^c



Expert Systems with Applications (2012,39:1;54-60)

UYGULAMALAR

- Otomatik Retina Taraması
- Klinik Karar Desteđi
- Tahmini Nüfus Risk Sınıflandırması
- Genomik
- Hasta Self-Monitör Araçları
- Tele Sağlık Uygulamaları
- Diğer Cihazlar (Diyet ve Egzersiz)

Otomatik Retina Taraması

- FDA, dijital retina görüntülerini analiz etmek ve retinopatinin erken saptanmasına yardımcı olmak için bir Yapay Zeka algoritması kullanan bir cihaz olan IDx-DR'yi Nisan 2018'de onayladı
- ADA diyabet bakımında yapay zekanın kullanımını desteklemektedir
- Diyabetik retinopati ve maküler ödemin tespiti için otonom yapay zekanın kullanımını kabul etmiştir

Yapay Zeka Kullanan Software Programı IDx-DR

IDx-DR for Diabetic Retinopathy Screening

PDF PRINT COMMENTS

MARGOT SAVOY, MD, MPH, FAAFP, CPE, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

Am Fam Physician. 2020 Mar 1;101(5):307-308.


IDx-DR is a software program that uses artificial intelligence (AI) to analyze retinal images taken with the Topcon TRC-NW400, a fully automated nonmydriatic retinal camera designed to obtain high-resolution color images of the retina and the anterior segment of the eye. It is approved by the U.S. Food and Drug Administration for diabetic retinopathy screening in adults 22 years and older with diabetes mellitus.

TEST	INDICATION	POPULATION, AGE RANGE, AND FREQUENCY	COST*
IDx-DR	Screening for diabetic retinopathy	Adults 22 years and older with diabetes mellitus who have no history of diabetic retinopathy† Annual unless retinopathy detected	Patient: \$101 Practice: The Topcon TRC-NW400 camera costs approximately \$15,000 to \$22,000 IDx-DR software (the fee charged per analyzed image is unavailable)

*—Payment rate according to Healthcare Bluebook and Lombart Instrument Co.
†—This is the population indicated for IDx-DR software use. It is not indicated for diabetic retinopathy screening in general.



BMJ Open Use of smartphones for detecting diabetic retinopathy: a protocol for a scoping review of diagnostic test accuracy studies

Choon Han Tan ,¹ Willie-Henri Quah,² Colin S H Tan,³ Helen Smith,⁴ Lorainne Tudor Car¹

To cite: Tan CH, Quah W-H, Tan CSH, *et al.* Use of smartphones for detecting diabetic retinopathy: a protocol for a scoping review of diagnostic test accuracy studies. *BMJ Open* 2019;**9**:e028811. doi:10.1136/bmjopen-2018-028811

ABSTRACT

Introduction Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus and the leading cause of impaired vision in adults worldwide. Early detection and treatment for DR could improve patient outcomes. Traditional methods of detecting DR include the gold standard Early Treatment Diabetic Retinopathy Study seven standard fields fundus photography, ophthalmoscopy and slit-lamp biomicroscopy. These modalities can be

Strengths and limitations of this study

- ▶ This is a protocol for a scoping review that aims to provide evidence to inform the use of smartphone ophthalmoscopy in patients with diabetes mellitus.
- ▶ Our findings may be of particular relevance to clinicians in rural or resource-constrained settings with limited access to standard diagnostic approaches

Klinik Karar Desteđi

- Tip 2DM'lilerde insülin sonrası kısa ve uzun vadeli HbA1c yanıtını tahmin etmek için
- Makine öğrenimi tabanlı klinik karar destek araçları geliştirildi
- Hastanın HbA1c yanıtını etkileyebilecek deęişkenleri de tanımlar
- İlaç tedavisine uyumu düzenler
- Hastaneye yatma riskini tahmin etmek için bir yaklaşım geliştirebilir

RESEARCH ARTICLE

Development of a clinical decision support system for diabetes care: A pilot study

Livvi Li Wei Sim¹, Kenneth Hon Kim Ban¹, Tin Wee Tan¹, Sunil Kumar Sethi², Tze Ping Loh^{2*}

¹ Department of Biochemistry, National University of Singapore, Singapore, ² Department of Laboratory Medicine, National University Hospital, Singapore

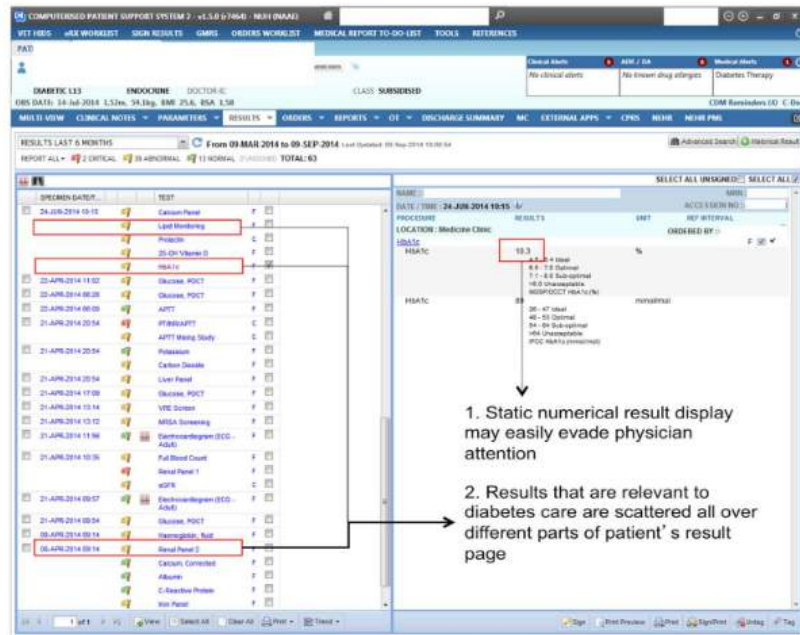


Fig 1. A screenshot of Computerized Patient Support System 2 showing the HbA_{1c} result of a patient as an example. The left panel displays a list of all the historical laboratory and radiological tests ordered for a patient. The right panel displays the results of the individual test order on the left panel.

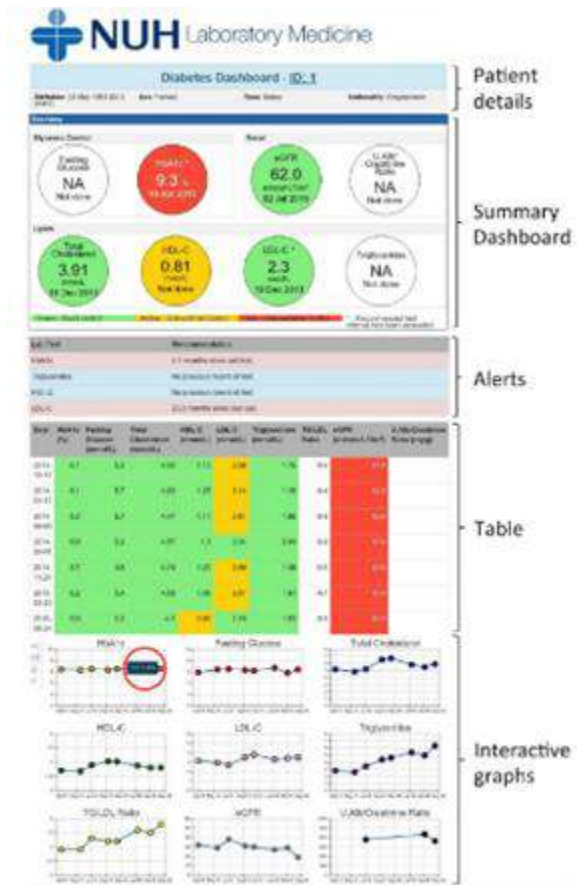


Fig 2. A screenshot of the summary dashboard, alerts, table and interactive graphs in the Diabetes Dashboard. An example of the hover tool is shown, displaying the test result of the individual point in the HbA_{1c} graph when the mouse hovers over it (boxed in red).

Tahmini Nüfus Risk Sınıflandırması

Makine öğrenimini kullanan sağlık hizmeti öneri sistemi

- Hastanın yaşam tarzını
- Fiziksel sağlık faktörlerini
- Zihinsel sağlık faktörlerini
- Sosyal ağ faaliyetlerini

analiz ederek **diyabete yönelik hastalık riskini tahmin etmeye** yardımcı olur

- Diyabetiklerde komplikasyon gelişme olasılığına ilişkin tahminler oluşturmak için tahmine dayalı modeller oluşturulur

Bu tür birçok model diyabetin;

- Hem uzun vadeli (örneğin retinal, kardiyovasküler ve renal)
- Hem de kısa vadeli (örneğin hipoglisemi)

komplikasyonlarının gelişimini tahmin etmek için geliştirilmiştir

- Ayak görüntülerini yorumlamak ve **diyabetik ayak ülserlerinin gelişimini** değerlendiren mobil uygulamalar vardır
- **Gestasyonel diyabetli gebelerde tip 2 diyabet gelişiminin tahmini için** modeller vardır

The Machine Learning help fight Type 2 diabetes.



Traditional Risk Prediction Models

- Successful Examples
 - ARIC
 - KORA
 - FRAMINGHAM
 - AUSDRISC
 - FINDRISC
 - San Antonio Model
- Easy to ask/measure in the office, or for patients to do online
- Simple model: can calculate scores by hand

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age
 0 p. Under 45 years
 2 p. 45-54 years
 3 p. 55-64 years
 4 p. Over 64 years

2. Body mass index (See reverse of form)
 0 p. Lower than 25 kg/m²
 1 p. 25-29 kg/m²
 3 p. Higher than 30 kg/m²

3. Waist circumference measured below the navel (usually at the level of the navel)
 MEN
 0 p. Less than 94cm
 2 p. 94-102cm
 4 p. More than 102cm
 WOMEN
 0 p. Less than 80cm
 2 p. 80-88cm
 4 p. More than 88cm

4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (excluding normal daily activity)?
 0 p. Yes
 2 p. No

5. How often do you eat vegetables, fruit or berries?
 0 p. Every day
 1 p. Not every day

6. Have you ever taken anti-hypertensive medication regularly?
 0 p. No
 2 p. Yes

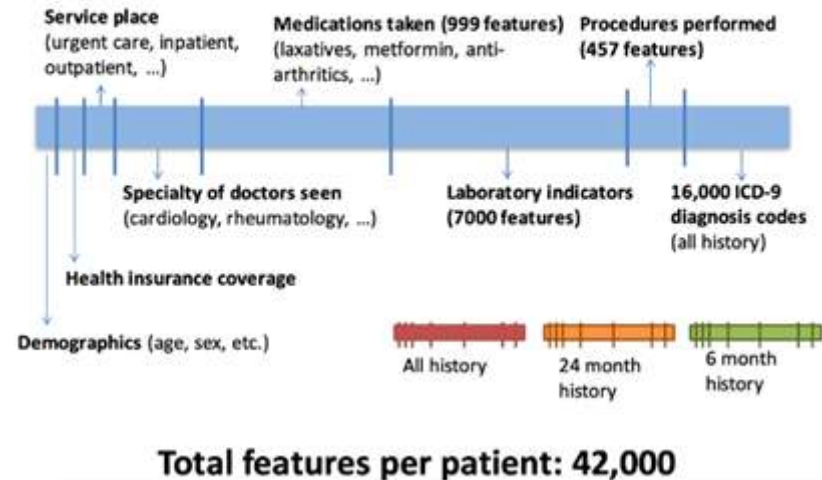
7. Have you ever been found to have high blood glucose (e.g. in a health examination, during an illness, during pregnancy)?
 0 p. No
 5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (Type 1 or Type 2)?
 0 p. No
 3 p. Yes: grandparent, aunt, uncle or first cousin (but not own parent, brother, sister or child)
 5 p. Yes: parent, brother, sister or own child

Total risk score
 The risk of developing type 2 diabetes within 10 years is:
 Lower than 7: Low: estimated 1 in 100 will develop disease
 7-11: Slightly elevated: estimated 1 in 25 will develop disease
 12-14: Moderate: estimated 1 in 6 will develop disease
 15-20: High: estimated 1 in 3 will develop disease
 Higher than 20: Very high: estimated 1 in 2 will develop disease

Please take care!

Features used in models



Article

Deep Learning Classification for Diabetic Foot Thermograms [†]

Israel Cruz-Vega ¹, Daniel Hernandez-Contreras ², Hayde Peregrina-Barreto ^{3,*}, Jose de Jesus Rangel-Magdaleno ² and Juan Manuel Ramirez-Cortes ²

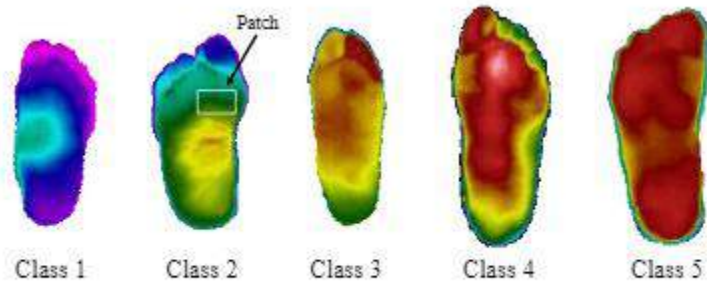


Figure 1. Images of the five level grades of the thermograms.

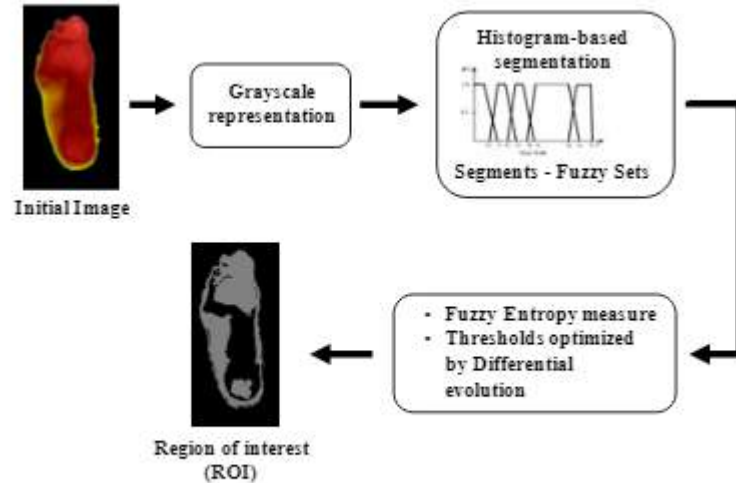


Figure 2. Automatic segmentation process

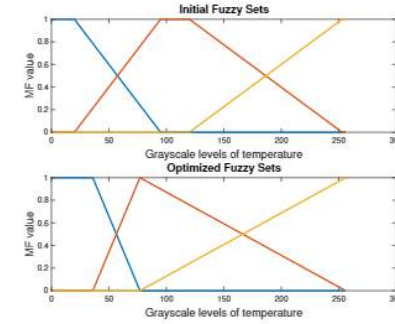


Figure 5. Fuzzy sets of the segmentation process in a DM foot with the optimal value of two thresholds

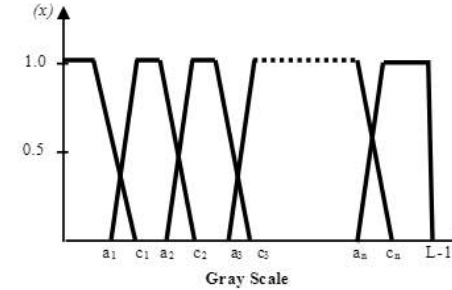


Figure A1. Fuzzy membership function for *n*-level thresholding

$$\mu_1(k) = \begin{cases} 1 & k \leq a_1 \\ \frac{k-c_1}{a_1-c_1} & a_1 \leq k \leq c_1 \\ 0 & k > c_1 \end{cases}$$

$$\mu_{n-1}(k) = \begin{cases} 0 & k \leq a_{n-2} \\ \frac{k-a_{n-2}}{c_{n-2}-a_{n-2}} & a_{n-2} < k \leq c_{n-2} \\ 1 & c_{n-2} < k \leq a_{n-1} \\ \frac{k-c_{n-1}}{a_{n-1}-c_{n-1}} & a_{n-1} < k \leq c_{n-1} \\ 0 & k > c_{n-1} \end{cases}$$

$$\mu_n(k) = \begin{cases} 1 & k \leq a_{n-1} \\ \frac{k-a_n}{c_n-a_n} & a_{n-1} \leq k \leq c_{n-1} \\ 1 & k > c_{n-1} \end{cases}$$

The maximum fuzzy entropy for each of the *n*-level segments

Genomik

Genom Çalışmaları ;

- Diyabete genetik yatkınlığı belirleyen, potansiyel 400'den fazla sinyal tanımlamıştır
- Nöral Network Modeller ile pankreas adacık hücreleri için;
- Çoklu genom haritalaması
- Düzenleyici epigenomik çalışmalar yapılabilir

Mikrobiyal Belirleyici Genlerin Mikrobiyom Verileri;

- Diyabet gelişme olasılığını tahmin etmek
- Doğrulanmış diyabeti olan hastalarda tedaviye rehberlik etmek için kullanılabilir

Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps

We expanded GWAS discovery for type 2 diabetes (T2D) by combining data from 898,130 European-descent individuals (9% cases), after imputation to high-density reference panels. With these data, we (i) extend the inventory of T2D-risk variants (243 loci, 135 newly implicated in T2D predisposition, comprising 403 distinct association signals); (ii) enrich discovery of lower-frequency risk alleles (80 index variants with minor allele frequency <5%, 14 with estimated allelic odds ratio >2); (iii) substantially improve fine-mapping of causal variants (at 51 signals, one variant accounted for >80% posterior probability of association (PPA)); (iv) extend fine-mapping through integration of tissue-specific epigenomic information (islet regulatory annotations extend the number of variants with PPA >80% to 73); (v) highlight validated therapeutic targets (18 genes with associations attributable to coding variants); and (vi) demonstrate enhanced potential for clinical translation (genome-wide chip heritability explains 18% of T2D risk; individuals in the extremes of a T2D polygenic risk score differ more than ninefold

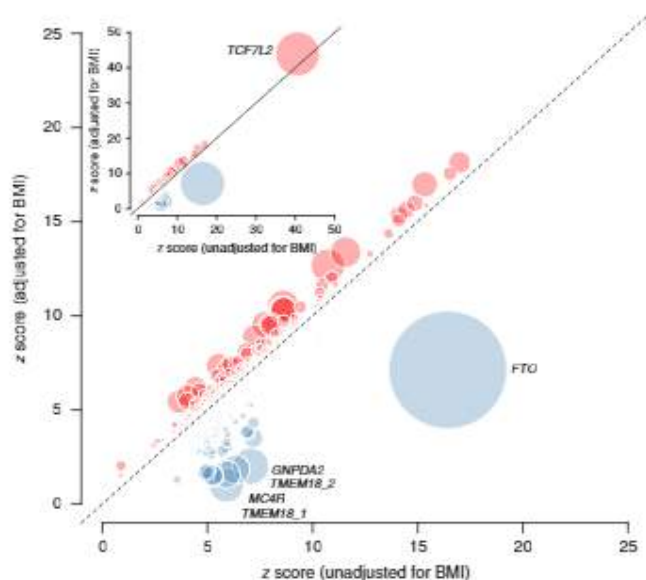


Fig. 2 | Comparison of estimated T2D effect sizes between BMI-adjusted and unadjusted models. z scores for each of the 403 distinct signals from BMI-unadjusted analysis (50,791 cases and 526,121 controls; x axis) are plotted against the z scores from the BMI-adjusted analysis (50,402 cases and 523,888 controls; y axis). Variants displaying higher T2D effect sizes in BMI-adjusted analyses are shown in red, and variants with higher T2D effect sizes in BMI-unadjusted analyses are shown in blue. Circle diameter is proportional to $-\log_{10}$ heterogeneity *P* value (two-tailed test). Inset presents the same plot with *TCF7L2* variant included.

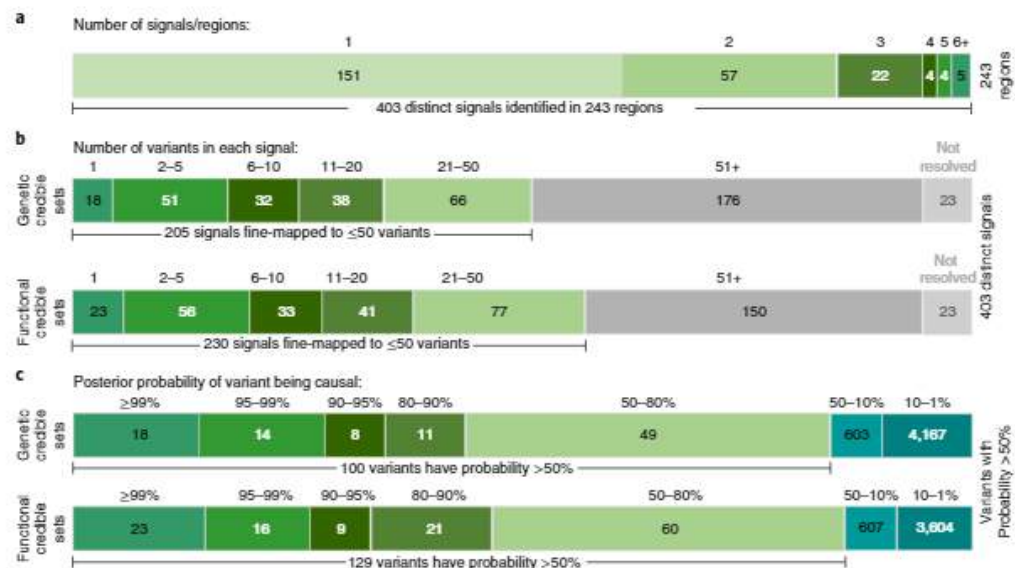


Fig. 3 | Summary of fine-mapped associations. **a**, Distinct association signals. A single signal at 151 loci, and two to ten signals at 92. **b**, Number of variants in genetic and functional 99%-credible sets. Eighteen and 23 signals were mapped to a single variant in genetic and functional credible sets, respectively. **c**, Distribution of the PPA of the variants in credible sets. Four of the 51 variants with PPA >80% in the genetic credible sets have lower PPAs in the functional credible set, thus giving a total of 73 variants with PPA >80% in either.

Hasta Self-Monitör Araçları

- Kendi kendine yönetim, diyabet tedavisinin anahtarıdır.

Yapay zekanın ortaya çıkmasıyla birlikte hastalar;

- Kendi diyabetlerini yönetme
- Kendi parametreleri için veri üretme
- Kendi sağlık uzmanları olma

yetkisine kavuştu.

Artan farkındalık:

- Dijital platformlar diyabetlilerin hedeflenen eğitimine olanak tanır
- Web tabanlı programlar
- Cep telefonu ve akıllı telefon uygulamalar

Hasta Self-Monitör Araçları

Kendi kendine tedavi:

- Yapay zeka diyabetlilerin diyet ve aktivite için günlük kararlar almasına izin verir
- Uygulamalar, hastaların gıda alımının kalitesini ve kalori değerini değerlendirmesine izin vermek için kullanılabilir

Dijital terapötikler :

- **Dijital koçluk**; bir uygulama aracılığıyla dijital bir müdahale (FareWell)
- Tip 2 diyabetli 118 kişiye 12 hafta telefonla destek verildi
- Çalışmanın sonunda katılımcıların % 92'sinden olumlu geribildirim alındı.
- **One Drop Mobile uygulaması**; kendi kendine bakımı izlemek için diyabet destek programı
- 1288 tip 1 ve tip 2 diyabetli hastada 4 ay boyunca denendi HbA1c'de %1,07 ila %1,27 mutlak düşüş bildirildi.

BUSINESS

OF LIFE STYLE MEDICINE

Mark A. Berman, MD, Kevin J. Appelbaum, BSE,
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FareWell and the How of Lifestyle Medicine

Abstract: *The what of Lifestyle Medicine, including a whole foods dietary pattern, has been well established, but the how has remained elusive. How do we apply what we know in a cost-effective and widely accessible manner to prevent, treat, and even reverse chronic disease? Over the decade ahead, we believe the field of Lifestyle Medicine and the people who need it most will benefit from addressing the how. This article summarizes the founding and operational principles of FareWell Inc. - a digital therapeutics company targeting lifestyle-related cardiometabolic diseases. We outline our current use of mobile health technology and artificial intelligence and describe our early clinical experience, business model, and key anticipated challenges.*

including advanced coronary artery disease, type 2 diabetes, hypertension, hyperlipidemia, and early-stage prostate cancer.¹⁻⁴ Despite these advances, access to lifestyle medicine interventions remains low and chronic disease rates continue to rise globally. This reflects

internet access, wearable devices, machine learning, and online social communities. Similarly, the development of the health coaching profession provides an army of relatively low-cost health care professionals that can facilitate behavior change in a patient-centric model.


 Over the past decade, new technologies have emerged that may enable more scalable, cost-effective lifestyle medicine models. 

both the potency of the root causes—the physical and cultural environment that produces chronic disease—and the difficulty in scaling lifestyle medicine models of care. Several barriers to scaling interventions are well appreciated, but

Digital Therapeutics Target Chronic Disease Through Diet and Lifestyle

At FareWell, we are creating novel digital therapeutics targeting lifestyle-related

Design and Development of Diabetes Management System Using Machine Learning

Robert A. Sowah ¹, Adelaide A. Bampoe-Addo,¹ Stephen K. Armoo,¹ Firibu K. Saalia,² Francis Gatsi,³ and Baffour Sarkodie-Mensah¹

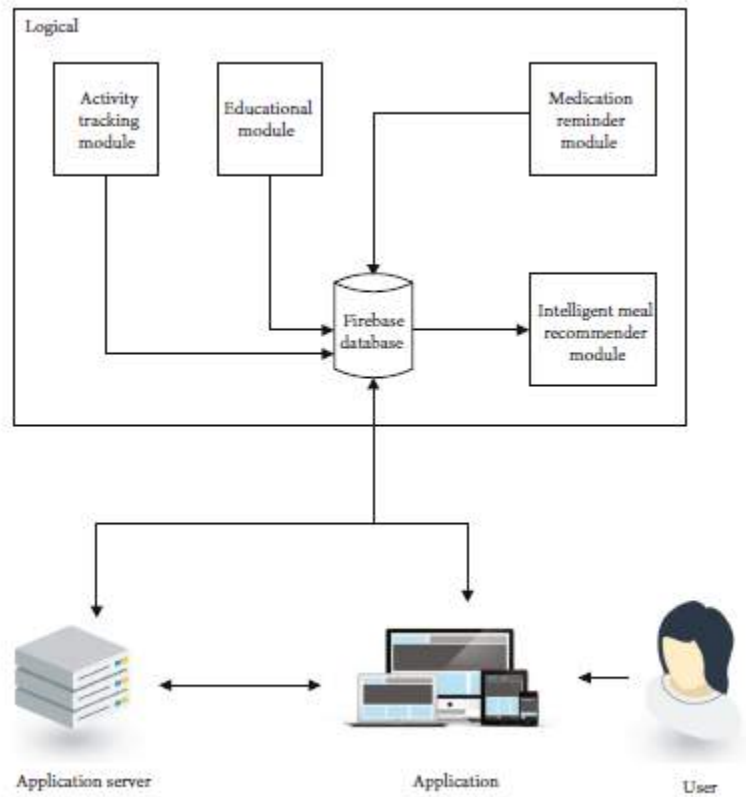


FIGURE 1: System architecture for the implemented system with all submodules.

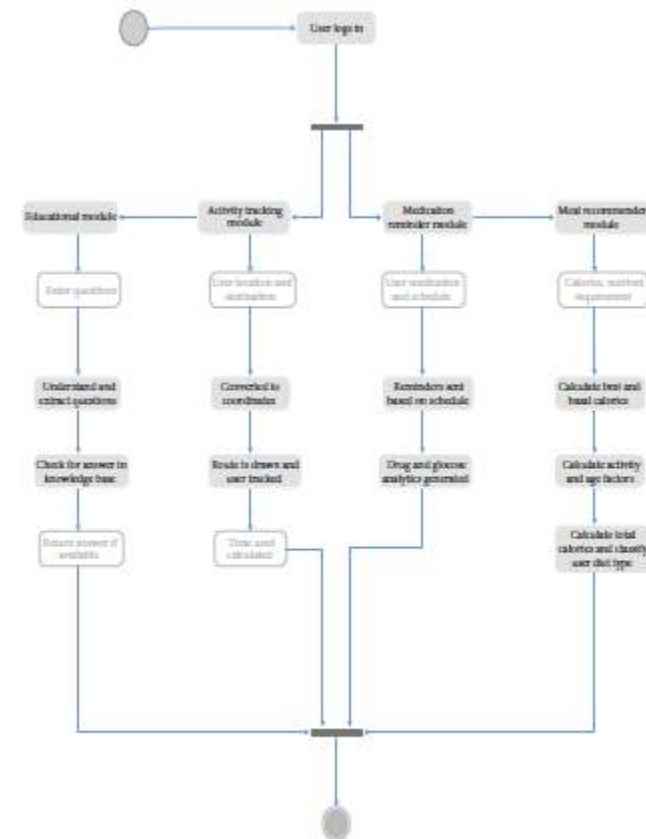


FIGURE 2: The activity flow diagram for the implemented system architecture.

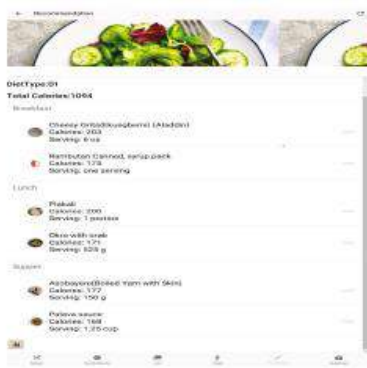


FIGURE 9: Meal recommendation with the caloric content and amount of serving.

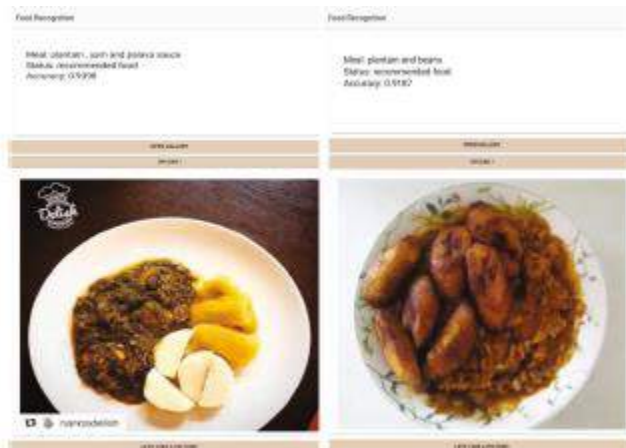


FIGURE 10: Testing the food recognition model with local dishes.

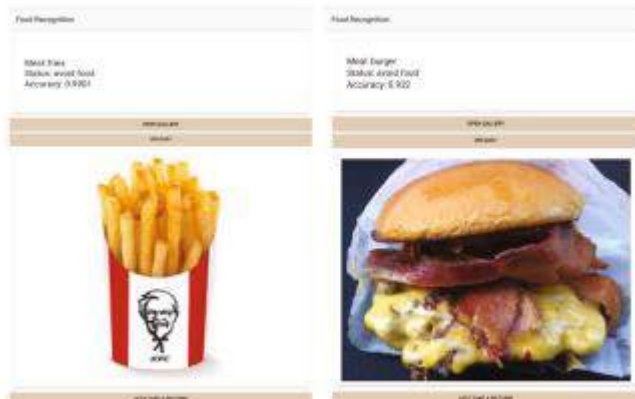


FIGURE 12: Testing the food recognition model for fries and cheeseburger.



FIGURE 14: Testing question and answer bot.



FIGURE 15: Glucose readings on mobile phone for diabetes management.

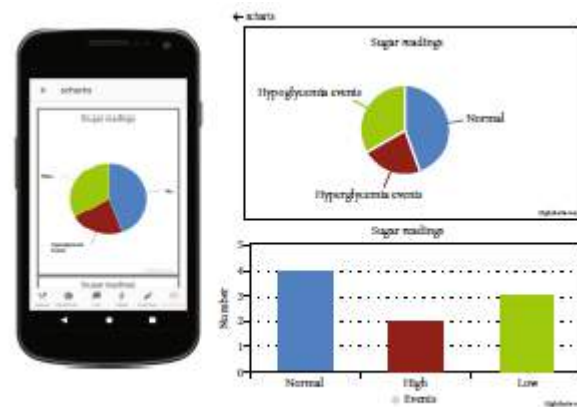


FIGURE 16: Charts of Glucose reading to track progress on a daily, monthly, or yearly level.

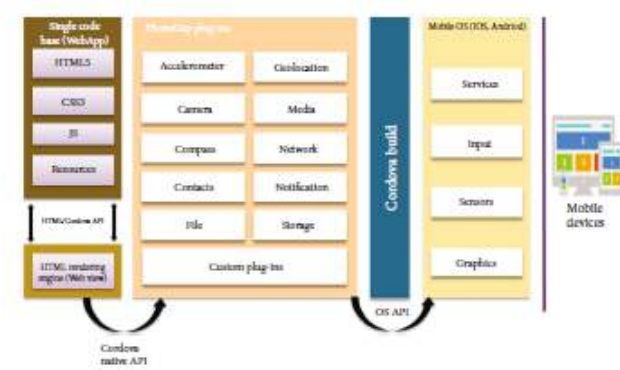


FIGURE 8: Architecture for Cordova plugin.

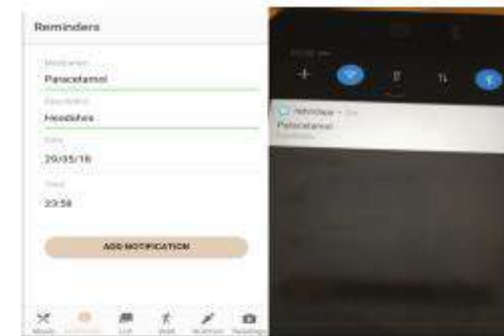


FIGURE 17: Notification and Reminders for taking medications.

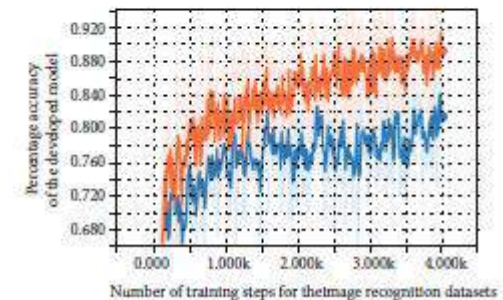


FIGURE 18: Accuracy of the model of the inception model.

DİYABET EĞİTİMİNDE YAPAY ZEKA UYGULAMALARI

TABLE 1 | Examples of the most representative publications on AI applied to diabetes education.

Method	Application	Description	References
SVM ML	Diabetes prediction	SVM are recently one of the most popular and flexible ML algorithms used for classification, they are being used to discover valuable knowledge from large databases such as to test the feasibility of using data collected in electronic medical records for development of effective models for diabetes risk forecasting. But the approach is tolerant to a reasonable number of false positives.	(24, 25)
ANN DL	Diet Guidance Retinopathy assessment Exercise guidance	The most widely used techniques are artificial neural networks (ANNs). ANN are based on interconnected neurons, that means, the human brain function. A deep learning algorithm (DL), can be considered and evolution of ANN. For example, based on the techniques of ANN, then proposed a regression model that could be used to automatically analyze the exercise levels of patients wearing accelerometers and heart monitors and monitor changes in glucose levels that occurred while the subjects were exercising.	(28, 30, 32, 33) (50, 51) (34)
CBR	Insulin dose recommendation	Case-based reasoning (CBR) is used to calculate an individualized insulin bolus using an insulin intravenous bolus calculator, thereby achieving optimal glucose levels in patients and optimizing insulin treatment. CBR learns from experiences of past similar meals, which are described in cases through a set of parameters (e.g., time of meal, exercise). However, there are some limitations of CBR, as its application needs to get a large sample size and is often excessively time-consuming.	(39, 41)
GA	Blood sugar monitoring Foot ulcer prediction	GA simulates natural selection by creating a population of individuals (solutions) for optimization problems. Recently this technique is applied on the early detection of foot ulcers. This methodology involves three steps: segmentation, geometric transformation, and asymmetry analysis.	(43, 44) (52, 53)
FL ES	Hypoglycemia detection Peripheral neuropathy	ES are defined as systems with the ability to capture expert knowledge and facts. Fuzzy systems are one of the most common ES used in the field of diabetes. It is a new version of expert systems that uses fuzzy logic for data processing and a self-adaptive learning algorithm.	(40, 45) (54)
DT	Diabetes management	DT is most often created based on a learning algorithm. By recording information on diet, exercise, pharmaceutical use, and blood sugar levels, the application of DL in the systems can combine patient- and physician-support tools for the purpose of improving disease outcomes.	(46, 48, 49)

